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Office of Chemical Safety and
Pollution Prevention

Summary of External Peer Review and Public Comments and Disposition for Carbon Tetrachloride (Methane, Tetrachloro-)

CASRN: 56-23-5

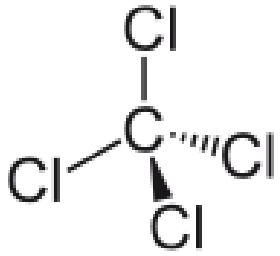

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Table of Contents

This document summarizes the public and external peer review comments that the EPA's Office of Pollution Prevention and Toxics (OPPT) received for the risk evaluation of carbon tetrachloride (CCl4). It also provides EPA/OPPT's response to the comments received from the public and the peer review panel.

EPA/OPPT appreciates the valuable input provided by the public and peer review panel. The input resulted in numerous revisions to the hazard summary.

Peer review charge questions[1] are used to categorize the peer review and public comments into specific issues related to the five main themes.

1. Environmental Fate and Exposure
2. Environmental Hazard and Risk Characterization
3. Occupational Exposure and Releases
4. Human Health Effects
5. Human Health Risk Characterization
6. Content and Organization

All peer review comments for the six charge questions are presented first, organized by charge question in the following section. These are followed by the public comments. For each theme, general comments pertaining to all chemicals are presented first, and then additional comments pertaining to only one or several chemicals follows.

ABBREVIATIONS

ACC	American Chemistry Council
ACR	Acute to chronic ratio
AF	Assessment factor
AEGL	Acute Exposure Guideline Levels
AOP	Adverse outcome pathway
APF	Assigned protection factor
ATSDR	Agency for Toxic Substances and Disease Registry
$BMCL_{10}$	Benchmark concentration lower bound
BMD	Benchmark dose
BMDL	Benchmark dose lower bound
BMDS	Benchmark Dose Software
CAA	Clean Air Act
CASRN	Chemical Abstracts Service Registry Number
CDR	Chemical Data Reporting
CFR	Code of Federal Regulations
CI	Confidence Interval
CNS	Central Nervous System
COC	Concentration of concern
CRED	Criteria for Reporting and Evaluating ecotoxicity Data

[1] These are the questions that EPA/OPPT submitted to the panel to guide the peer review process.

CWA	Clean Water Act
DMR	Discharge Monitoring Report
DNA	Deoxyribonucleic acid
DT_{50}	Time at which the amount of compound is degraded by half
EC_{10}	Effect Concentration at which 50% of test organisms exhibit the effect
EC_{50}	Effect Concentration at which 50% of test organisms exhibit the effect
ECOTOX	EPA's ECOTOXicology knowledgebase
EDC	Ethylene dichloride
EDF	Environmental Defense Fund
E-FAST	Exposure and Fate Assessment Screening Tool
EPA	United States Environmental Protection Agency
EPI Suite™	Estimation Programs Interface suite of models
EPN	Environmental Protection Network
GWAS	Genome-wide association studies
GWP	Global warming potential
HAP	Hazardous air pollutant
HBCD	hexabromocyclododecane, representing the cyclic aliphatic bromide cluster
HEC	Human equivalent concentration
HERO	Health & Environmental Research Online
HFC	Hydrofluorocarbons
HFO	Hydrofluoro-olefines
HSIA	Halogenated Solvents Industry Alliance
IARC	International Agency for Research on Cancer
IOM	Institute of Medicine
IPCS	International Programme on Chemical Safety
IUR	Inhalation unit risk
JBRC	Japan Bioassay Research Center
K_{oc}	Soil Organic Carbon-Water Partitioning Coefficient
K_{ow}	Octanol-Water Partitioning Coefficient
LC_{10}	Lethal Concentration at which 10% of test organisms die
LC_{50}	Lethal Concentration at which 50% of test organisms die
LD_{10}	Lethal Concentration at which 10% of test organisms die
LMS	Linearized Multistage Model
LOAEL	Lowest Observed Adverse Effect Level
LOD	Limit of detection
MACT	Maximum Achievable Control Technology
MAK	Maximale Arbeitsplatzkonzentration, or the "maximum permissible concentration of a substance as a gas, vapour or aerosol in the air at the workplace"
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
MOA	Mode of Action
MOE	Margin of Exposure
MP	Montreal Protocol
NAS	National Academies of Science
NASEM	National Academies of Sciences, Engineering, and Medicine
NATA	National Air Toxics Assessment

NEI	National Emissions Inventory
NHANES	National Health and Nutrition Examination Survey
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
NOAEL	No Observed Adverse Effect Level
NOEC	No Observed Effect Concentration
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NTTC	National Tribal Toxics Council
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
OES	Occupational exposure scenario
OHAT	Office of Health Assessment and Translation
OPPT	Office of Pollution Prevention and Toxics
ONU	Occupational non-user
OSHA	Occupational Safety and Health Administration
PBPK	Physiologically based pharmacokinetic
PDM	Probabilistic Dilution Model
PECO	Populations, Exposures, Comparators, and Outcomes
PEL	Permissible exposure limits
PESS	Potentially exposed or susceptible subpopulations
PF	Protection factor
POD	Point of departure
PPE	Personal protective equipment
ppm	Parts per million
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QSAR	Quantitative Structure-Activity Relationship
RCRA	Resource Conservation and Recovery Act
RE	Risk Evaluation
RESO	Receptor, Exposure, Setting (or Scenario), and Outcome
RQ	Risk quotient
SACC	Science Advisory Committee on Chemicals
SCHF	Safer Chemicals Healthy Families
SDS	Safety Data Sheet
SDWA	Safe Drinking Water Act
SEG	Similar Exposure Groups
SOP	Standard Operating Procedures
SR	Systematic Review
SSD	Species sensitivity distributions
STORET	STOrage and RETrieval database
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	Time-weighted average
UF	Uncertainty factor
UF_A	Interspecies uncertainty/variability factor
UF_H	Intraspecies uncertainty/variability factor

USGS	U.S. Geological Survey
VOC	Volatile organic compound
WHO	World Health Organization
WOE	Weight-of-evidence

List of Comments		
#	**Docket File**	**Submitter**
22	EPA-HQ-OPPT-2019-0499-0022	Christopher Bevan, Director, Scientific Programs, Halogenated Solvents Industry Alliance, Inc. (HSIA)
23	EPA-HQ-OPPT-2019-0499-0023	Jonathan Kalmuss-Katz, Staff Attorney, Earthjustice et al.
26	EPA-HQ-OPPT-2019-0499-0026	Richard A. Denison, Lead Senior Scientist, Environmental Defense Fund (EDF)
27	EPA-HQ-OPPT-2019-0499-0027	Anonymous public comment
28	EPA-HQ-OPPT-2019-0499-0028	Environmental Investigation Agency (EIA)
29	EPA-HQ-OPPT-2019-0499-0029	Christopher Bevan, Director, Scientific Programs, HSIA
30	EPA-HQ-OPPT-2019-0499-0030	Michelle Roos, Environmental Protection Network (EPN)
31	EPA-HQ-OPPT-2019-0499-0031	Suzanne Hartigan, Senior Director, Regulatory and Technical Affairs, American Chemistry Council (ACC)
32	EPA-HQ-OPPT-2019-0499-0032	Liz Hitchcock, Director, Safer Chemicals Healthy Families (SCHF) et al.
33	EPA-HQ-OPPT-2019-0499-0033	Jennifer Sass, Senior Scientist, Natural Resources Defense Council (NRDC)
37	EPA-HQ-OPPT-2019-0499-0037	Amy McCamphill, Senior Counsel, and Amy Chyao, Assistant Corporation Counsel, Environmental Division, New York City Law Department
38	EPA-HQ-OPPT-2019-0499-0038	Randy Rabinowitz, Executive Director, Occupational Safety & Health Law Project and Jonathan Kalmuss-Katz and Lakendra Barajas, Staff Attorneys, Earthjustice
39	EPA-HQ-OPPT-2019-0499-0039	Christopher Bevan, Director, Scientific Programs, HSIA
40	EPA-HQ-OPPT-2019-0499-0040	J. Warshaw
41	EPA-HQ-OPPT-2019-0499-0041	Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco (UCSF PRHE) et al.
42	EPA-HQ-OPPT-2019-0499-0042	Dianne C. Barton, Chair, National Tribal Toxics Council (NTTC)
43	EPA-HQ-OPPT-2019-0499-0043	Liz Hitchcock, Director, SCHF et al.
44	EPA-HQ-OPPT-2019-0499-0044	Liz Hitchcock, Director, SCHF et al. (Attachments)
45	EPA-HQ-OPPT-2019-0499-0045	Suzanne Hartigan, Senior Director, Regulatory and Technical Affairs, ACC
SACC	N/A	Science Advisory Committee on Chemicals (SACC)

Environmental Fate and Exposure		
Charge Question 1.1: Please comment on the data, approaches and/or methods used to characterize exposure to aquatic receptors.		
#	**Summary of Comments for Specific Issues Related to Charge Question 1**	**EPA/OPPT Response**
Fate assumptions/models		
SACC	**SACC COMMENTS:** Several Committee members suggested the need to consistently use an appropriate environmental fate model (*e.g.*, similar to fugacity level 3) with realistic inputs (emissions to water and air) to determine when a log K_{oc} value is low enough to ignore sorption to sediment and a Henry's law constant is high enough to ignore all other fate processes but volatilization.	Added to section 2.1.2 Fate and Transport: "EPI Suite™ (U.S. EPA, 2012a) module that estimates volatilization from lakes and rivers ("WVol") was run using inputs to evaluate the volatilization half-lives of CCl_4 in various compartments. Given the measured vapor pressure of 115 mm Hg at 20°C and a calculated Henry's law constant of 2.76×10^{-2} atm-m^3/mol, these physical-chemical property inputs to the WVol model in EPI Suite indicates that CCl_4 will volatilize from a model river with a half-life on the order of 1.3 hours and from a model lake on the order of approximately 5 days. Although volatilization is expected to be rapid, a Level III Fugacity model predicted that when CCl_4 is continuously released to water, 80% of the mass will partition to water, 19% to air, <1% to soil and < 1% to sediment. Level III fugacity modeling results are impacted by which compartments (air, water or soil) receive the chemical releases so a second scenario was run assuming equal releases of CCl_4 to all three compartments. The model predicted that when CCl_4 is continuously released to air, water, and soil, 50% of the mass partitions to water, 47.3% to air, 2.5% to soil and < 1% to sediment. Intermittent releases of CCl_4 are not expected to result in long-term presence in the aquatic compartment."
SACC	**SACC COMMENTS:** • Several members indicated that complete biodegradation (mineralization) was unlikely to occur	Added to section 2.1.2 Fate and Transport: "Studies have shown the formation of degradation products

	under most environmental conditions. The potential for the formation of products including chloroform, methylene chloride, methyl chloride, and phosgene should be discussed (see example flow diagram by Tripp et al., 2020). Recommendation: Include a discussion of metabolic pathways and environmental breakdown products.	such as chloroform, methylene chloride, methyl chloride, and phosgene under various environmental conditions. Under sulfate reducing conditions, partial complete dechlorination of carbon tetrachloride has been observed (de Best et al., 1997). Carbon tetrachloride has been found to degrade under anaerobic conditions to methane, carbon dioxide and carbon monoxide through various metabolic pathways (Van Eekert et al., 1998). Additionally, abiotic transformation has been observed to play an important role in degradation of carbon tetrachloride to carbon disulfide, however substitutive and oxidative dechlorination processes forming carbon dioxide from degradants may pose as a potential pathway to producing safe degradation products (Van Eekert et al., 1998).”
SACC	**SACC COMMENTS:** One member found the discussion of whether CCl4 wastes are in the form of mixed liquids or as residues mixed into solid wastes to be inadequate, as physical form affects emissions and exposure estimates.	For Engineering: See Section 2.4.1.7.9. This section details the disposal of carbon tetrachloride including information on the form of the wastes for assessing emissions and exposures of carbon tetrachloride.
23, 26	**PUBLIC COMMENTS:** EPA dismissed phosgene exposures because TRI data do not show releases of CCl4 and phosgene at the same facility. At least one facility that reported releases of CCl4 under the NEI also reported phosgene emissions under the NEI and phosgene manufacture under the Chemical Data Reporting (CDR). Other sources of data, such as the NEI, should be considered before excluding a potential exposure.	During problem formulation, EPA identified information on the thermal decomposition of carbon tetrachloride into phosgene, a highly toxic gas. However, thermal decomposition of carbon tetrachloride is more likely to occur in open environments and less likely in the type of closed systems used during the manufacturing and processing of carbon tetrachloride. Because exposures to the general population from any thermal decomposition of carbon tetrachloride would occur via exposure pathways that fall under the jurisdiction of other EPA-administered laws, such exposures are not within the scope of the risk evaluation.

		EPA acknowledges that the SABIC Alabama facility reported both carbon tetrachloride and phosgene to TRI. A facility could have these chemicals (both phosgene and carbon tetrachloride) onsite, but their co-existence does not imply that the phosgene is present due to the decomposition of carbon tetrachloride. Additional clarifications are indicated below: 1. A site reported to TRI that the carbon tetrachloride is manufactured as an impurity. It is not revealed which process the carbon tetrachloride is manufactured as an impurity. This facility involves a chlor-alkali process, that produces chlorine. Chlorine is used in several other on-site processes. This site also produces hydrochloric acid (HCl). SABIC, as a company, produces ethylene dichloride (EDC, also known as 1,2-dichloroethane) and vinyl chloride monomer (VCM), which are both sold as a product and used internally (EDC used to make VCM, and VCM used to make PVC). Thus, there could be a number of processes that use both chlorine and carbon-based compounds to produce carbon tetrachloride as an impurity (*e.g.*, the production of phosgene, VCM, EDC). EPA has also exercised its authority in TSCA Section 6(b)(4)(D) to exclude from the scope of this risk evaluation conditions of use associated with carbon tetrachloride generated as a byproduct. Carbon tetrachloride generated as a byproduct during the manufacture of 1,2-dichloroethane will be assessed in the risk evaluation for 1,2-dichloroethane (see Final Scope of the Risk Evaluation for 1,2-Dichloroethane, EPA-HQ-OPPT-2018-0427-0048). 2. The phosgene is typically manufactured to be used on-site as a reactant due to its properties and toxicity. Phosgene is not typically transported across the U.S. The specific site could be producing the phosgene to use as a reactant to produce

		polycarbonate (which is one of the polymer products of this company). Phosgene is well known as a reactant that, with bisphenol A, is used to produce polycarbonate. Considering the above two items, there is no reason to think the phosgene is present as a decomposition product of carbon tetrachloride, especially when the CDR and TRI reports the phosgene is intentionally manufactured as a site-limited reactant. Decomposition of carbon tetrachloride requires ≥ 730°C, a temperature at which phosgene could form from carbon tetrachloride (Noweir et al., 1973). However, phosgene, typically formed otherwise, is not stable at temperatures above 250°C, decomposes to form mixtures of carbon monoxide, chlorine, carbon dioxide, and carbon tetrachloride (ACC, 2018).
26	**PUBLIC COMMENTS:** EPA cited no sources to demonstrate that decomposition of CCl4 is "more likely" to occur in open systems, which EPA alleges will not happen because CCl4 is only manufactured and processed in closed systems. EPA does not explain how releases to the environment of CCl4 would not decompose and result in exposures to phosgene. The SACC should call on EPA to address its failure to consider CCl4's decomposition into phosgene and any resulting exposures to phosgene.	Carbon tetrachloride storage and handling are reported to be performed in close and secure vessel (OxyChem, 2014). In addition, samples could only be collected (potential release source) from the closed systems that have built-in capabilities to handle vents, provide nitrogen, process unused liquid volume and results in a sample in a closed container (OxyChem, 2014). (OxyChem, 2018) reported closed loop unloading systems are designed to minimize solvent vapor emissions during transfer by exchanging the liquid solvent in the trailer with the storage tank vapors. In addition, it was also reported that the closed system cuts the water usage (resource needs) and release of carbon tetrachloride (Cheremisinoff and Rosenfeld, 2009). Carbon tetrachloride has no flash point, it is not flammable. Decomposition of carbon tetrachloride requires ≥ 730°C, a temperature at which phosgene could form from carbon

		tetrachloride (ACC, 2018). However, phosgene, typically formed otherwise, is not stable at temperatures above 250°C, decomposes to form mixtures of carbon monoxide, chlorine, carbon dioxide, and carbon tetrachloride (ACC, 2018). Because exposures to the general population from any decomposition of carbon tetrachloride would occur via exposure pathways that fall under the jurisdiction of other EPA-administered laws, such exposures are not within the scope of the risk evaluation. The revised risk evaluation document has also included the following sentences: "Carbon tetrachloride should be stored in labelled, airtight containers in a well-ventilated place protected from light and at a temperature below 30°C. It must be stored separated from chemically active metals. Disposal of carbon tetrachloride contaminated wastes via incineration is not recommended due to the non-flammability of carbon tetrachloride and to the formation of phosgene, hydrogen chloride and other toxic gases on heating."
Presentation of physical-chemical and fate properties		
SACC	**SACC COMMENTS:** Instances of incorrect terminology were noted: • CCl4 is referred to as moderately miscible (p. 25, line 299). A compound is either miscible in water or not. It cannot be partially miscible. • The risk evaluation states that CCl4 is expected to volatilize based on its high vapor pressure (p. 25, line 297). Vapor pressure is related to intermolecular interactions, whereas volatilization depends on interactions between CCl4 molecules and the	Replaced section 1.1 Physical and Chemical Properties with: "Physical-chemical properties influence the environmental behavior and the toxic properties of a chemical, thereby informing the potential conditions of use, exposure pathways and routes and hazards being evaluated. A summary of the physical and chemical properties of carbon tetrachloride are listed in Table 1-1. Carbon tetrachloride is a colorless liquid at room temperature with a sweet, aromatic and ethereal odor resembling chloroform (Merck, 1996); (U.S. Coast Guard, 1985). It is water miscible, has a melting point of -23 °C, a

	environmental phases it is in contact with, along with environmental conditions.	boiling point of 76.8 °C and its' density is 1.4601 g/cm^3 at 20°C (Lide, 1999). Carbon tetrachloride has a Henry's Law Constant of 0.0276 atm m^3/mole and a log K_{ow} value of 2.83(Leighton and Calo, 1981); (Hansch et al., 1995). Other pertinent physical-chemicals properties are listed below in Table 1-1." The language regarding miscibility was changed to state that carbon tetrachloride is "water miscible." Volatilization is further discussed in section 2.1 Fate and Transport. Additional detail was added on the level of volatilization that is estimated to occur form different environmental phases and under different environmental conditions.
SACC	**SACC COMMENTS:** Recommendation: Better define the quality and variability associated with physical-chemical properties. • The discussion on data quality assessment and variability for physical-chemical and fate properties, including those obtained from EPA's EPI Suite™ (both experimental and estimated values), should be expanded. Several SACC members suggested estimating confidence intervals (CIs) around each property and conducting a sensitivity analysis to determine if variability would change the outcome of the quality pathway analysis.	Due to the differences among study conditions, generating confidence intervals for each property would be very complex. However, the range and quality of available data was considered in the fate assessment of carbon tetrachloride. The sources used to collect physical-chemical property data for carbon tetrachloride were all subjected to data quality evaluations based on metrics presented in the *Application of Systematic Review in TSCA Risk Evaluations* document, and the full data quality assessments are presented in a supplemental file.
SACC	**SACC COMMENTS:** When more than one estimation method is available in EPI Suite™, the estimation method that was used should be specifically stated and the rationale for selecting one estimation method over another should be provided. The quality of the estimated value should be based on the	When multiple values are available, EPA presents the range of values. Additional language regarding the use of EPI Suite™ is provided in section 2.1 of the risk evaluation. EPA employs guidance located in the EPI Suite User's Manual and help files, along with scientific judgment to make decisions on endpoint applicability. This suggestion will be considered

	reliability of the estimation method.	further as we continue to develop our systematic review process.
Current releases		

28, 32, 43	**PUBLIC COMMENTS:**
	• The EPA draft risk evaluation reports that, according to TRI data, U.S. air emissions for reporting facilities totaled over 176,000 pounds in 2018. The 2016 Stratosphere-troposphere Processes And their Role in Climate (SPARC) Report on the Mystery of Carbon Tetrachloride concludes that the scale of emissions of CCl4 is several orders of magnitude higher than TRI data suggest. The SPARC report estimated total CCl4 emissions of 20±5 Gg/year, narrowing, but not eliminating, the gap with top down estimates.
	  • CCl4 is produced as a co-product of PCE production or as a co-product of CM production. In total, the combined emissions of CCl4 from PCE and CM plants, or unreported non-feedstock uses, is 13 Gg.
	  • CCl4 is widely used as a feedstock to manufacture hydrofluorocarbons (HFCs) and its production and use is expected to expand further to produce their replacements, unsaturated HFCs or hydrofluoro-olefines (HFOs). CCl4 production for these so-called 'nondispersive' applications globally totaled ~200 Gg in 2012-2014 based on which bottom-up emissions contributions of 2 Gg/year from feedstock use have been derived.
	  • The production and use of CCl4, and thus potential emissions of CCl4 in chlor-alkali
		The SPARC report is an important reference addressing global sources and sinks of carbon tetrachloride. EPA acknowledged in the final risk evaluation the global sources of carbon tetrachloride in the atmosphere including feedstock uses and non-feedstock emissions. Please see revised paragraph in Section 1.2 (line 1187 – 1196). The revision includes various carbon tetrachloride sources and their emissions. The reasonably available information includes citations of peer-reviewed articles used to inform global sources of carbon tetrachloride. Assessing global emissions of carbon tetrachloride is outside the scope of the risk evaluation.
		
		EPA did not include the emission pathways to ambient air from commercial and industrial stationary sources, because stationary source releases of carbon tetrachloride to ambient air are under the jurisdiction of Section 112 of CAA. In addition, carbon tetrachloride production and use are controlled under the 1987 Montreal Protocol. Resulting exposures were out of scope as described in section 1.4.3 of the final risk evaluation for carbon tetrachloride.
		
		Under TSCA section 6(b), EPA is required to determine whether a chemical substance presents unreasonable risks without consideration of costs or other non-risk factors. Consideration of technically and economically feasible alternative substances is a step that may occur as part of a potential risk management action developed pursuant to TSCA section 6(c)(2)(C). This type of analysis could be considered as part of a subsequent risk management action if

	facilities, constitutes up to ~10 Gg of emissions each year. There is no recognized alternative to CCl4 in chlor-alkali production, and no foreseeable end to the use of CCl4 as a feedstock or chemical intermediary. • While production of CCl4 continues, illegal trade and use of CCl4 is expected to persist. Recent use of CCl4 as a feedstock has been linked to unexpected emissions of CFC-11, and its widespread illegal production and use in China, and with observed concentrations of CCl4 emissions in the same region where the increased emissions of CFC-11 were observed. In eastern Europe, Georgia and Armenia have seized illegal CCl4 entering the European Union (EU) from Russia. While these incidences were, in theory, nondispersive, illegal dispersive uses of CCl4 production have also been recorded. EPA must consider all available scientific information regarding observed global and regional emission trends and concentrations of CCl4 when considering these risks, and not rely solely on industry reported data. We urge EPA to evaluate and subsequently further regulate CCl4 production and intermediate uses under TSCA to avoid unreasonable risk to human health and the environment.	unreasonable risk is determined and regulatory considerations are pursued. The illegal production, trade, and use of carbon tetrachloride in Asia and Europe are not conditions of use because these activities are not known, intended, or reasonably foreseen to occur in the United States. EPA assumes compliance with existing laws and regulations, including those applicable to the production, trade, and use of carbon tetrachloride, and EPA has no evidence that these illegal materials are being manufactured (including imported) here. Clarifying language about what pathways are under the jurisdiction of other EPA-administered statutes has been added to Section 1.4.3 of the Risk Evaluation. Assessing global emissions of carbon tetrachloride is outside the scope of the risk evaluation
SACC, 26, 28, 30, 32, 28	**SACC COMMENTS** Table E-1 indicates a >300-pound release from one facility in 2014 and a 14-pound spill from another facility in 2015. How many spills per year occur in the population of 49 facilities? If the average is 1 per year, then analysis of releases should factor in these occurrences. **PUBLIC COMMENTS:**	Spills and leaks generally are not included within the scope of TSCA risk evaluations because in general they are not considered to be circumstances under which a chemical substance is intended, known or reasonably foreseen to be manufactured, processed, distributed, used, or disposed of. To the extent there may be potential exposure from spills and leaks, EPA is also declining to evaluate environmental

	EPA states that environmental spills are not within the scope of the risk evaluation and were thus not evaluated. This exclusion is contrary to TSCA's mandate that EPA evaluate the conditions of use of a chemical substance.
	• "Conditions of use" under TSCA mean "the circumstances, … under which a chemical substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of." Spills are a "reasonably foreseen" aspect of the circumstances under which CCl4 is manufactured, processed, distributed, used, or disposed of.
	• Spills and leaks are undoubtedly reasonably foreseeable, and indeed, when preparing environmental impact statements (EISs) for federal projects, the federal government regularly analyzes the potential for spills and leaks because they are reasonably foreseen aspects of such projects.
	• EPA cites two instances of known spills: a San Diego spill that exceeded permit limits and a Dover Chemical Corp. spill in 2014. These spills are known conditions of use that result in actual exposures to people and the environment.
	  • In 2016 and 2017, a 200% increase in CCl4 emissions above 2015 levels was reported, coming from a facility owned by Dover Chemical Corporation. This is the same facility where a large accidental spill of 'chlorinated wax material' containing CCl4 byproduct occurred from a reactor in 2014, leading to concerns about EPA's voluntary reporting program.
	  • Table 4-2 in the EPA draft reports that "San Diego Sea World facility (CA0107336) was not included
		exposure pathways addressed by other EPA-administered statutes and associated regulatory programs.
		
		First, EPA does not identify carbon tetrachloride spills or leaks as "conditions of use." EPA does not consider carbon tetrachloride spills or leaks to constitute circumstances under which carbon tetrachloride is manufactured, processed, distributed, used, or disposed of, within TSCA's definition of "conditions of use." Congress specifically listed discrete, routine chemical lifecycle stages within the statutory definition of "conditions of use" and EPA does not believe it is reasonable to interpret "circumstances" under which carbon tetrachloride is manufactured, processed, distributed, used, or disposed of to include uncommon and unconfined spills or leaks for purposes of the statutory definition. Further, EPA does not generally consider spills and leaks to constitute "disposal" of a chemical for purposes of identifying a condition of use in the conduct of a risk evaluation.
		
		In addition, even if spills or leaks of carbon tetrachloride could be considered part of the listed lifecycle stages of carbon tetrachloride, EPA has "determined" that spills and leaks are not circumstances under which carbon tetrachloride is intended, known or reasonably foreseen to be manufactured, processed, distributed, used, or disposed of, as provided by TSCA's definition of "conditions of use," and EPA is therefore exercising its discretionary authority under TSCA section 3(4) to exclude carbon tetrachloride spills and leaks from the scope of the carbon tetrachloride risk evaluation. The exercise of that authority is informed by EPA's experience in developing scoping documents and risk evaluations, and on various TSCA provisions indicating the

	in the analysis since the reported level is above permit discharge limits; noncompliance and spills are not in the scope of this risk evaluation." Given the relevance of the 2016 Lautenberg TSCA amendment and Ninth Circuit finding that EPA should no longer be ignoring spills, it might be worthwhile to inquire whether those understandings also apply to NPDES permit discharge limits. • EPA does not evaluate occupational exposures from spills and other accidental releases of CCl4. The SACC should comment on EPA's failure to consider this condition of use.	intent for EPA to have some discretion on how best to address the demands associated with implementation of the full TSCA risk evaluation process. Specifically, since the publication of the Risk Evaluation Rule, EPA has gained experience by conducting ten risk evaluations and designating forty chemical substances as low- and high-priority substances. These processes have required EPA to determine whether the case-specific facts and the reasonably available information justify identifying a particular activity as a "condition of use." With the experience EPA has gained, it is better situated to discern circumstances that are appropriately considered to be outside the bounds of "circumstances… under which a chemical substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of" and to thereby meaningfully limit circumstances subject to evaluation. Because of the expansive and potentially boundless impacts that could result from including spills and leaks as part of the risk evaluation (*e.g.*, due to the unpredictable and irregular scenarios that would need to be accounted for, including variability in volume, frequency, and geographic location of spills and leaks; potential application across multiple exposure routes and pathways affecting myriad ecological and human receptors; and far-reaching analyses that would be needed to support assessments that account for uncertainties but are based on best available science), which could make the conduct of the risk evaluation untenable within the applicable deadlines, spills and leaks are determined not to be circumstances under which carbon tetrachloride is intended, known or reasonably foreseen to be manufactured, processed, distributed, used, or disposed of, as

		provided by TSCA's definition of "conditions of use." Exercising the discretion to not identify spills and leaks of carbon tetrachloride as a condition of use is consistent with the discretion Congress provided in a variety of provisions to manage the challenges presented in implementing TSCA risk evaluation. See *e.g.*, TSCA sections 3(4), 3(12), 6(b)(4)(D), 6(b)(4)(F). In particular, TSCA section 6(b)(4)(F)(iv) instructs EPA to factor into TSCA risk evaluations "the likely duration, intensity, frequency, and number of exposures under the conditions of use…," suggesting that activities for which duration, intensity, frequency, and number of exposures cannot be accurately predicted or calculated based on reasonably available information, including spills and leaks, were not intended to be the focus of TSCA risk evaluations. And, as noted in the preamble to the Risk Evaluation Rule, EPA believes that Congress intended there to be some reasonable limitation on TSCA risk evaluations, expressly indicated by the direction in TSCA section 2(c) to "carry out [TSCA] in a reasonable and prudent manner." For these reasons, EPA is exercising this discretion to not consider spills and leaks of carbon tetrachloride to be conditions of use. Second, even if carbon tetrachloride spills or leaks could be identified as exposures from a condition of use in some cases, these are generally not forms of exposure that EPA expects to consider in risk evaluation. TSCA section 6(b)(4)(D) requires EPA, in developing the scope of a risk evaluation, to identify the hazards, exposures, conditions of use, and potentially exposed or susceptible subpopulations

		the Agency "expects to consider" in a risk evaluation. This language suggests that EPA is not required to consider all conditions of use, hazards, or exposure pathways in risk evaluations. EPA has chosen to tailor the scope of the risk evaluation to exclude spills and leaks in order to focus analytical efforts on those exposures that present the greatest potential for risk. In the problem formulation documents for many of the first 10 chemicals undergoing risk evaluation, EPA applied the same authority and rationale to certain exposure pathways, explaining that "EPA is planning to exercise its discretion under TSCA 6(b)(4)(D) to focus its analytical efforts on exposures that are likely to present the greatest concern and consequently merit a risk evaluation under TSCA...." This approach is informed by the legislative history of the amended TSCA, which supports the Agency's exercise of discretion to focus the risk evaluation on areas that raise the greatest potential for risk. See June 7, 2016 Cong. Rec., S3519-S3520. In addition to TSCA section 6(b)(4)(D), the Agency also has discretionary authority under the first sentence of TSCA section 9(b)(1) to "coordinate actions taken under [TSCA] with actions taken under other Federal laws administered in whole or in part by the Administrator." TSCA section 9(b)(1) provides EPA authority to coordinate actions with other EPA offices, including coordination on tailoring the scope of TSCA risk evaluations to focus on areas of greatest concern rather than exposure pathways addressed by other EPA-administered statutes and regulatory programs, which does not involve a risk determination or public interest finding under TSCA section 9(b)(2). EPA has already

		tailored the scope of this risk evaluation using such discretionary authorities with respect to exposure pathways covered under the jurisdiction of other EPA-administered statutes and associated regulatory programs (see section 1.4.3). Following coordination with EPA's Office of Land and Emergency Management (OLEM), EPA has found that exposures of carbon tetrachloride from spills and leaks fall under the jurisdiction of RCRA. See 40 CFR 261.33(d) (defining in part a hazardous waste as "any residue or contaminated soil, water or other debris resulting from the cleanup of a spill into or on any land or water of any commercial chemical product or manufacturing chemical intermediate having the generic name listed [40 CFR 261.33(e) or (f)], or any residue or contaminated soil, water or other debris resulting from the cleanup of a spill, into or on any land or water, of any off-specification chemical product and manufacturing chemical intermediate which, if it met specifications, would have the generic name listed in [40 CFR 261.33(e) or (f)]"); 40 CFR 261.33(f) (listing carbon tetrachloride as hazardous waste no. U211). As a result, EPA believes it is both reasonable and prudent to tailor the TSCA risk evaluation for carbon tetrachloride by declining to evaluate potential exposures from spills and leaks, rather than attempt to evaluate and regulate potential exposures from spills and leaks under TSCA. EPA has evaluated disposal as a condition of use of carbon tetrachloride with respect to occupational exposures from disposal activities. Regarding regulatory action, EPA must evaluate all the

		conditions of use it expects to consider under TSCA in the risk evaluation and propose risk management for any condition of use which the Agency determines presents unreasonable risk in the final risk evaluation. Risk management activities are outside the scope of the risk evaluation. As the commenter indicated, for any condition of use determined to have unreasonable risk, EPA will consider this and other comments during risk management. EPA has clarified Sea World carbon tetrachloride discharges. EPA has estimated the surface water concentration from Sea World carbon tetrachloride releases using a proxy facility in San Diego since Sea World permit data was not available in E-FAST2014. The Risk Evaluation has been revised to include these surface water carbon tetrachloride estimate results. The Risk Evaluation has also been revised to include a greater explanation of the E-FAST 2014 modeling approach, model calculations, inputs and results.
26	**PUBLIC COMMENTS:** 26 • EPA "expects insignificant or unmeasurable concentrations of CCl4 in the manufactured chlorinated substances in the commercially available products." The only corroborating sources that it provided were qualified comments, with no data, from representatives of the chemical industry asserting that levels are low.	EPA has no reasonably available information indicating the presence of carbon tetrachloride in commercially available products in concentrations at significant or measurable levels. In addition, the high volatility of carbon tetrachloride and the extent of reaction and efficacy of the separation/purification process for purifying final products supports EPA's assumption that there are insignificant or unmeasurable concentrations in these products. While carbon tetrachloride is used in the manufacturing of other chlorinated compounds that may be subsequently added to commercially available products, EPA expects that consumer use of such products would present only de minimis exposure to, or otherwise insignificant risk from, carbon tetrachloride given the high volatility of carbon

		tetrachloride and the extent of reaction and efficacy of the separation/ purification process for purifying final products. No additional information was received by EPA following the publication of the problem formulation that would update the problem formulation conclusion that carbon tetrachloride is expected to be present in consumer products at trace levels resulting in de minimis exposures or otherwise insignificant risks and therefore that consumer uses do not warrant inclusion in the risk evaluation. For that reason, EPA exercised its discretionary scoping authority under TSCA sec. 6(b)(4)(D) to exclude this use from the scope of the risk evaluation in order to focus the Agency's analytical efforts on those exposures that are likely to present the greatest concern. See section 1.4.2.2 of the Risk Evaluation; sections 2.2.2 and 2.2.2.1 of the Problem Formulation of the Risk Evaluation for Carbon Tetrachloride (May 2018); 82 FR 33736, 33729 (July 20, 2017).
Legacy releases		
23, 26, 30, 32, 42, 43	**PUBLIC COMMENTS:** In the 2017 Scoping document, EPA stated, "In the case of CCl4, legacy uses and associated legacy disposals will be excluded from the scope of the risk evaluation." • Disposal is a condition of use that must be considered in a TSCA risk evaluation. A decision in the U.S. Court of Appeals for the Ninth Circuit issued in late 2019 found that legacy activities should NOT be excluded from the definition of conditions of use and should be analyzed during risk evaluations. • EPA's SACC noted that EPA failed to consider releases associated with disposal.	EPA has determined that general population exposures due to drinking water contamination, ambient-water contamination, and disposal pathways are regulated under other statutes and are outside the scope of this risk evaluation. See section 1.4.3 of the risk evaluation. EPA did not identify any "legacy uses" or "associated disposals" of carbon tetrachloride, as those terms are described in EPA's Risk Evaluation Rule, 82 FR 33726 (July 20, 2017). Therefore, no such uses or disposals were added to the scope of the risk evaluation for carbon tetrachloride following the issuance of the opinion in *Safer Chemicals, Healthy Families v. EPA*, 943 F.3d 397 (9th Cir. 2019).

	The Agency further stated that "As a result of this phase-out and ban, it is highly unlikely that there are any ongoing uses of CCl4 that could be considered legacy uses, and no such uses have been evaluated." • The SPARC Report estimated that up to 10 Gg/year of global CCl4 emissions is likely from legacy emissions from contaminated soils and toxic waste treatment facilities. • According to the latest TRI data, in 2018, >73,000 pounds of CCl4 were released to land through underground injection, disposal in hazardous waste landfills, and "other land disposal." According to 2017 TRI data, total CCl4 production-related waste totaled 36,838,580 pounds, of which 26,838,850 underwent treatment. Landfills and other waste-treatment operations reported environmental releases accounting for 34% of total CCl4 releases. • ATSDR indicates that CCl4 was detected in soil at 103 National Priorities List (NPL) hazardous waste sites, in sediment at 23 NPL hazardous waste sites, in groundwater at 310 NPL hazardous waste sites, and in surface water at 53 NPL sites. • EPA has detected CCl4 inside homes above or around Superfund sites where CCl4 was found in the groundwater, indicating a potential vapor intrusion pathway. • The Agency is obligated to revise this draft risk evaluation to incorporate the assessment of any identified legacy uses and then re-issue updated assessment for further peer review and public comment. In particular, The National Tribal Toxics Council (NTTC) strongly urges that environmental release from waste management sites, including	The use of carbon tetrachloride in the past are not "legacy" uses. As described in EPA's Risk Evaluation Rule (82 FR 33726 (July 20, 2017)), a legacy use is an ongoing use of a chemical substance in a particular application where the chemical substance is no longer being manufactured, processed, or distributed in commerce for that application. The example provided in the Rule is insulation, which may be present in buildings after a chemical substance is no longer being made for that use. In contrast, the uses of carbon tetrachloride phased out as a result of the Montreal Protocol and CAA Amendments of 1990 as well as the uses banned by CPSC in 1970 (excluding unavoidable residues not exceeding 10 ppm atmospheric concentration) are no longer being manufactured, processed, distributed in commerce, used, or disposed of, to the best of EPA's knowledge, which is based on EPA's research and outreach. Specifically, EPA received no information from any commenters or otherwise indicating that products in the United States had been stockpiled or that use or disposal was ongoing. Therefore, carbon tetrachloride uses that have been phased out or banned are not conditions of use because they are not known, intended, or reasonably foreseen.

	transfer sites, construction and demolition sites, materials recovery facilities, and landfills be evaluated with consideration of unlined facilities with resulting leachate subsurface flow, ponded water, direct surface water and snowmelt runoff, ambient emissions from uncovered disposal areas, and untreated waste burning emissions.	
Future releases		
SACC, 28, 32, 43	**SACC COMMENTS:** The SACC is concerned about the trends in increasing CCl4 releases. The SACC report details several points of concern: • Data indicate that water releases are increasing in both quantity and fraction of total releases. • The National Air Toxics Inventory (2015) shows an increase in atmospheric CCl4 over a 10-year period. • The number of facilities with water releases is increasing. • The pattern of water releases is variable, but most facilities show an increasing trend. • Accidental releases are not considered in TSCA evaluations. • Smaller companies can manufacture/import/use slightly less than 10,000 pounds of CCl4 and dispose all of this without reporting to TRI. • Removal mechanisms (*i.e.*, biodegradation, photolysis in the troposphere) are likely too slow to prevent environmental concentrations of CCl4 from increasing. Overall, future releases, while uncertain, are expected to increase from current levels unless regulatory action is taken. **PUBLIC COMMENTS:** • CCl4 production in the U.S. is increasing due to	Clarifying language about what pathways are under the jurisdiction of other EPA-administered statutes, including pathways involving air and water releases, has been added to Section 1.4.3 of the Risk Evaluation. Water releases vary significantly between 2014 and 2018. EPA has revised Appendix E to also include surface water releases for 2019. The National Air Toxic Inventory (2015) data presents ambient air monitoring data for a number of chemicals including carbon tetrachloride. The risk evaluation did not consider the ambient air pathway due to its coverage under the of the Clean Air Act. Though some facilities show an increasing trend between the 2016 and 2018, there is considerable variability among the number of facilities discharging carbon tetrachloride and the amount of these releases over five years. Forty-nine facilities discharged carbon tetrachloride in 2017 whereas 42 in 2018 and 39 in 2019. In addition, many facilities discharge one or two years, then have zero releases other years. Therefore, two years of upward trend is not necessarily a predictor of future releases. It appears that total 2019 carbon tetrachloride

	growing demand for CCl4 as a feedstock in the manufacture of HFO refrigerants. Unregulated feedstock and intermediate uses of CCl4 are expected to increase by ≥50% in the near future. • U.S. production and import of CCl4 has already increased 10% from 129.1 million pounds in 2012 to 142.6 million pounds in 2015 according the CDR database.	releases decreased from 2018 to levels similar to 2017 confirming the variable nature of releases. EPA therefore averaged carbon tetrachloride releases over 5 years to capture this variability. EPA agrees with the SACC comment regarding limitations on the population of facilities manufacturing/importing/using and releasing carbon tetrachloride reflected in TRI. EPA therefore relied on the DMR data in EPA's ECHO database to capture releases to surface water. Please see comment response under "Current Conditions of Use and Emissions" for discussion of accidental releases." Carbon tetrachloride shows minimal susceptibility to indirect photolysis by hydroxyl radicals in the troposphere, where its estimated tropospheric half-life exceeds 330 years. Ultimately, carbon tetrachloride diffuses upward into the stratosphere where it is photodegraded to form the trichloromethyl radical and chlorine atoms (OECD, 2011). Carbon tetrachloride is efficiently degraded by direct photolysis under stratospheric conditions and the DT_{50} (Dissipation Time for 50% of the compound to dissipate) value is in the order of minutes. However, the troposphere to the stratosphere migration of carbon tetrachloride is very long and this migration time limits the dissipation. The rate of photodegradation increases at altitudes >20 km and beyond. Carbon tetrachloride dissolved in water does not photodegrade or oxidize in any measurable amounts, with a calculated hydrolysis half-life of 7,000 years based on experimental data at a concentration of 1 ppm (OECD, 2011). Removal mechanisms from water could include volatilization

		due to the Henry's Law constant and anaerobic degradation in subsurface environment. Domestic production and importation of carbon tetrachloride is currently prohibited under regulations implementing the Montreal Protocol (MP) and CAA Title VI, except when transformed (used and entirely consumed, except for trace quantities, in the manufacture of other chemicals for commercial purposes), destroyed (including destruction after use as a catalyst or stabilizer), or used for essential laboratory and analytical uses. (40 CFR Part 82, 60 FR 24970, 24971 (May 10, 1995).) Carbon tetrachloride is used and entirely consumed in feedstock and intermediate uses, and EPA does not believe rising emissions from these uses are likely. In any event, EPA determined that both the manufacture of carbon tetrachloride and the processing of that chemical as a reactant in the production of HFOs present an unreasonable risk of injury to the health of workers and ONUs, and will initiate TSCA section 6(a) risk management actions on these conditions of use as required under TSCA section 6(c)(1).

Mass balance assessment of releases		
SACC, 26, 43	**SACC COMMENTS:** Recommendation: Include a mass balance assessment of CCl4 released to the environment. • Several Committee members recommended using a table of the amounts of CCl4 manufactured/imported in the U.S., and the amounts used in processes/products, released to the environment, or recycled. This approach allows for better estimation of CCl4 discharges to the environment that are not captured in databases such as	EPA does not have reasonably available mass balance data to conduct such an analysis for carbon tetrachloride. EPA's analysis uses TRI and DMR to estimate the highest local per site water releases of carbon tetrachloride. The NEI, which is compiled every 3 years for the purpose of supporting residual risk evaluations as required by Section 112 of the CAA. NEI contains air emission estimates, which sites estimate using a variety of methods, such as emission factors, mass balance, stack monitoring. Purchase and disposal records are not

	TRI.	reported to NEI. However, NEI could not be used to reasonably estimate all media releases as it only includes air releases from larger facilities and would not include releases from many smaller shops that use carbon tetrachloride. EPA acknowledged in the revised Risk Evaluation the global sources of carbon tetrachloride in the atmosphere including feedstock uses and non-feedstock emissions (see responses below against #23, 30, 32, 43). Please see revised paragraph in Section 1.2 (line 1187 – 1196). The revision includes various carbon tetrachloride sources, their emissions and citations of peer-reviewed articles.
SACC	**SACC COMMENTS:** • The draft risk evaluation notes that CCl4 is used as a feedstock in the production of hydrochlorofluorocarbons, HFCs, HFOs, and perchloroethylene (multiple locations), and that production of HFC-245fa and HFC-365mfc accounted for 71% and 23%, respectively, of total CCl4 consumption in 2016 (p. 73). HFC-245fa and HFC-365mfc are being phased out as part of the EPA's Significant New Alternatives Policy (SNAP) program and usage of CCl4 for this condition of use is expected to decrease significantly. • A mass-balance accounting of the condition of use should be incorporated to better account for existing feedstock usages. • Mass balance estimated discharges could be used along with environmental fate models (*e.g.*, fugacity level 3 model) to supplement limited monitoring data. • Given the relatively long aerobic half-life of CCl4, if continual discharge is occurring, exposure to aquatic life would be ongoing and not require trophic transfer or bioaccumulation.	See above response regarding the hydrochlorofluorocarbons, HFCs, HFOs, and perchloroethylene, HFC-245fa and HFC-365mfc. Please refer response to mass-balance approach described earlier. EPA's evaluation of the conditions of use accounted for the existing feedstock usages and other published information as cited in the risk evaluation document. Level II fugacity model discussion included in Fate section of revised RE (section 2.1). Mass balance of releases of carbon tetrachloride, as reported by various researchers, has been discussed in the revised risk evaluation document. Appropriate citations are also included. EPA addressed exposure to aquatic life: environmental monitoring data were used to assess ambient water exposure to aquatic organisms. Details of these exposure estimates as compared to the aquatic toxicity benchmarks (concentrations of concern) are available in Section 4.1.2.

Uncertainty associated with modeled estimates		
SACC	**SACC COMMENTS:** Recommendation: Discuss the uncertainty associated with estimated exposures to aquatic organisms by the lack of monitoring data. • Monitoring data from EPA (1977) provide CCl4 concentrations in water downstream of five industrial facilities. The 92nd and 75th percentiles are higher than any 20-day estimate from the E-FAST and over 10 times higher than the 95th percentile of the 20-day predictions reported in the draft risk evaluation. These monitoring data should be included in this risk evaluation as a justification for using higher percentile E-FAST estimates, rather than the average.	EPA assessed facilities reporting monitoring data (DMRs) of carbon tetrachloride discharges and presents data over five years (2014 – 2018). These data are more representative of the environmental concentrations than monitoring values that predate many of the regulations placed on carbon tetrachloride (*e.g.*, CWA and CAA).
23, 43	**PUBLIC COMMENTS:** The draft risk evaluation states that "the literature search results for environmental exposures yielded 393 data sources. Of these data sources, none were determined to be relevant to the draft risk evaluation." EPA thus disregards all of the environmental exposure data in its possession, and instead calculates environmental risks based solely on modeling, as opposed to actual surface water, soil, and air concentrations. If EPA truly has no usable environmental exposure data, then it has the authority under TSCA to compel companies that manufacture, import, or use CCl4 to produce or generate such data. EPA's exclusive reliance on modeling, with no data to validate the results, does not provide a sufficient basis for the evaluation of CCl4's environmental risk.	EPA had sufficient information to complete the carbon tetrachloride risk evaluation using a weight of scientific evidence approach. EPA selected the first 10 chemicals for risk evaluation based in part on its assessment that these chemicals could be assessed without the need for regulatory information collection or development. The TSCA risk evaluation process does not require EPA to compel the generation of new data. In fact, in conducting a risk evaluation, EPA must "take into consideration . . . hazard and exposure information, under the conditions of use, that is reasonably available" (TSCA § 26(k)). When preparing this risk evaluation, EPA obtained and considered reasonably available information, defined in 40 CFR 720.33 as information that EPA possesses or can reasonably generate, obtain, and synthesize for use in risk evaluations, considering the deadlines for completing the evaluation. EPA has explained in its regulations that "EPA will use [information gathering] authorities on a case-by-case basis during the

		performance of a risk evaluation to obtain information as needed to ensure that EPA has adequate, reasonably available information to perform the evaluation" (40 CFR 702.41(b)(2)). As explained at 40 CFR 702.41(a)(7), "To the extent a determination as to the level of risk presented by a condition of use can be made using models or screening methodologies, EPA may determine that no further information or analysis is needed to complete its risk evaluation of the condition(s) of use." In this case, consistent with EPA's approach of conducting fit-for-purpose risk evaluations, described in greater detail in 82 FR 33726 at 33739-40 (July 20, 2017), EPA determined that a technically sound risk determination could be made, consistent with the best available science, without the generation of additional data (which, in any event, likely would not have been possible to produce and incorporate in the risk evaluation within the timeframe specified in TSCA section 6(b)(4)(G)). EPA used the peer-reviewed E-FAST model to estimate carbon tetrachloride surface water concentrations using facility monitoring and loadings data as reported to EPA in Discharge Monitoring Reports. EPA has high confidence in the model and the estimates of surface water concentrations given location-specific flow data and carbon tetrachloride discharge data. EPA will continue to improve on its method and data collection for the next round of chemicals to be assessed under TSCA.
45	**PUBLIC COMMENTS:** EPA applies a number of conservatisms to its environmental exposures estimates. While these approaches may suffice for screening level assessments, they do not represent real world exposures. For example, EPA used PDM within E-FAST 2014 to estimate surface	A refined analysis for the five sites that indicated risk to aquatic organisms has been added to section 4.1.2 and in the appendix (Table F-2). Briefly, EPA calculated surface water concentrations using E-FAST and associated, site-specific RQs to determine whether risk was or was not indicated at the five facilities that indicated risk during time periods relevant

	water concentrations. For situations where environmental exposures determined by E-FAST lead to a RQ >1.0, additional investigation about the site should be pursued. Worst-case assumptions in the model, such as no dilution during 7Q10 receiving stream flows or for the "still water body" scenario, may be unlikely. EPA should conduct a higher tier analysis of any facility for which it has concerns about exceedances based on the current approach.	to amphibian development. Risk was not indicated during time periods relevant to amphibian development at Eco Services Operations Facility (RQs < 1 for the three years where monitoring information was available). At the other four facilities for which a refined analysis was conducted, risk was indicated (RQs > 1) during the time periods relevant to amphibian development for at least 2 separate reporting periods.
Justification of exclusion of exposures regulated under other environmental statutes		
SACC	**SACC COMMENTS:** • EPA should provide additional documentation (*i.e.*, links to the specific environmental programs and statutes) that shows how other regulations will address terrestrial risk. • Releases to non-aqueous phases should be considered. At a minimum, a rationale should be added for exclusion of non-aqueous media. Recommendation: Improve the justifications/documentation for excluding non-aqueous media from consideration. • In the problem formulation, EPA indicated that CCl4 was identified in biosolids. This indicates that it will sorb to environmental solids and suggests that if CCl4 is discharged into streams, it is likely to be found in sediments. Therefore, stating that CCl4 discharged into streams rapidly distributes into air cannot be supported without monitoring data or a dynamic stream contaminant model that can predict distribution to water, air, and sediment. Recommendation: Be consistent and better define how physical-chemical properties and terminology are used to justify the exclusion of various	Section 1.4.3 in the final risk evaluation contains information on EPA administered regulatory programs and statutes with jurisdiction over exposure pathways to terrestrial ecological receptors from carbon tetrachloride emissions. A Level III fugacity model was assessed to investigate sorption to sediment. See section 2.1.2 Fate and Transport for narrative indicating the following: "Although volatilization is expected to be rapid, a Level III Fugacity model predicted that when carbon tetrachloride is continuously released to water, 80% of the mass will partition to water, 19% to air, <1% to soil and < 1% to sediment."

	environmental fate processes and distributions.	
26, 30, 32, 41, 42, 43	**PUBLIC COMMENTS:** The CCl4 draft lacks any assessment of risks to the general population or to the environment from CCl4's presence in air, water, and soil. EPA has excluded all general population risks from exposures due to releases of CCl4 to land, air, and water, based on the assumption that other statutes adequately address these exposures. Yet, no analyses or data have been presented to show that these other statutes are protective of the general population. Established scientific principles for exposure assessment require that known exposures (including from air, water, land, and all other pathways) be included in the assessment, or exposure will not be accurately quantified, and risk will be underestimated. The incorrect determination that emissions are not in scope is deeply concerning. Under TSCA, EPA must conduct a comprehensive assessment of exposures, and by failing to consider this pathway, EPA will miss potentially exposed or susceptible subpopulations (PESS) within the general population. The SACC has faulted EPA risk evaluations (1,4-dioxane, methylene chloride) for excluding environmental pathways of exposure. To justify this exclusion, EPA claims that it need not address "exposure pathways under programs of other environmental statutes" because they "adequately assess and effectively manage exposures" using "long-standing regulatory and analytical processes." • Risk evaluations under section 6(b)(4)(A) must determine "whether a chemical substance presents	As part of the Problem Formulation for carbon tetrachloride (U.S. EPA, 2018b), EPA found that exposures to the general population may occur from the conditions of use due to releases to air, water or land. The exposures to the general population via surface water, drinking water, ambient air and sediment pathways fall under the jurisdiction of other environmental statutes administered by EPA, *i.e.*, CAA, SDWA, CWA, and RCRA. As explained in more detail in section 1.4.3 of the final risk evaluation, EPA believes it is both reasonable and prudent to tailor TSCA risk evaluations when other EPA offices have expertise and experience to address specific environmental media, rather than attempt to evaluate and regulate potential exposures and risks from those media under TSCA. EPA believes that coordinated action on exposure pathways and risks addressed by other EPA-administered statutes and regulatory programs is consistent with the statutory text and legislative history, particularly as they pertain to TSCA's function as a "gap-filling" statute, and also furthers EPA aims to efficiently use Agency resources, avoid duplicating efforts taken pursuant to other Agency programs, and meet the statutory deadlines for completing risk evaluations. EPA has therefore tailored the scope of the risk evaluations for carbon tetrachloride using authorities in TSCA sections 6(b) and 9(b)(1). See section 1.4.3 of the Risk Evaluation. Clarifying language about what pathways are under the jurisdiction of other EPA-administered statutes has been added to Section 1.4.3 of the Risk Evaluation.

	an unreasonable risk of injury to health or the environment." This requirement cannot be met without examining all sources of exposure that contribute to health and environmental risk. • Section 6(b)(4)(A) provides that a risk evaluation must determine the substance's risks under "the conditions of use," defined as "the circumstances . . . under which a chemical substance is intended, known or reasonably foreseen to be manufactured, processed, distributed in commerce, used or disposed of." These "circumstances" clearly include environmental releases that result in pathways of human exposure, whether or not they might be controlled under other environmental laws. • If Congress had intended a blanket exemption for environmental releases from risk evaluations under section 6(b), it would have said so explicitly. But not only is there no such exemption in the law, its legislative history and structure demonstrate that Congress intended TSCA to provide a comprehensive framework for identifying and managing chemical risks, including those that derive from environmental exposure pathways subject to other environmental laws. Additional points: • EPA's position that other environmental laws should displace TSCA risk evaluations for all chemicals arbitrarily assumes that these laws provide equivalent protection of public health and the environment and that there is no added benefit in addressing environmental pathways of exposure	

	under TSCA. But these other laws vary greatly in the degree of protection that they afford against chemical risks and the extent of their application to unsafe chemicals. Many other laws do not regulate the entire universe of polluting sources. Other laws may impose controls based not on risk but on other considerations like cost or available technology. The CAA, SDWA, CWA, and RCRA are specific to individual media; they do not authorize an examination of exposure and risk across media. Other EPA authorities may lack the bandwidth to tackle serious chemical risks that do not represent immediate priorities if they are not mandated to do so. These limitations are why Congress gave EPA comprehensive authority over chemical risks under TSCA in 1976 and strengthened that authority in 2016. • EPA relies on the CAA to dismiss the need to assess exposures to CCl4 from air emissions. The standards under the CAA for HAPs are set for individual source categories, meaning that the exposures to CCl4 from all sources in combination are never considered. • In a recent proposed rule for a source category, EPA stated: "Although we are interested in placing source category and facility-wide HAP risk in the context of total HAP risk from all sources combined in the vicinity of each source, we are concerned about the uncertainties of doing so" (84 Fed. Reg. 58,268, 58,273). Thus, it is clear that EPA does not look at overall risk from a chemical substance in those assessments.	

	• Under the CAA, the first step is setting the Maximum Achievable Control Technology (MACT) standard, which does not require a risk evaluation. The mandate for the standard is to achieve the reduction in emissions possible, considering technology, costs, and energy requirements. • After the promulgation of the MACT standard, under the legal requirements for the CAA, it would take EPA 8 years to evaluate residual risk to the population and, if necessary, create a stricter standard; during the 8 years, people will continue to be exposed to harmful chemical levels. • Many of these other statutes require EPA or other agencies to consider factors such as cost and feasibility when setting standards – factors that TSCA explicitly forbids EPA from taking into account when assessing risks (Section 6(b)(4)(A)): "The Administrator shall …determine whether a chemical substance presents an unreasonable risk of injury …, without consideration of costs or other nonrisk factors." Extensive monitoring required by EPA showed exceedances of the EPA maximum contaminant level (MCL) and widespread contamination at levels that pose a cancer risk of >1 in one million and exceed the California public health goal (PHG). • In 1987, EPA set a maximum contaminant level goal (MCLG) of zero and an MCL of 5 μg/L. The MCL was based on the LOD for CCl4 in drinking water at the time. Subsequently developed	

	analytical methods can detect CCl4 at lower concentrations. • Some states recognize that the MCL should be lowered to assure health protection. California's Office of Environmental Health Hazard Assessment (OEHHA) set a PHG of 0.1 µg/L for CCl4 in drinking water in 2000. • The 2010 Integrated Risk Information System (IRIS) assessment for CCl4 determines that drinking water exposures over a lifetime to 0.5 µg/L – a tenth of the MCL – pose a cancer risk of 1 in a million. • The CCl4 problem formulation notes that: "Internal analysis for SYR3 (2006-2011) data…show that 118 of 55,735 systems (0.212%) have mean [drinking water] concentrations greater than the Minimum Reporting Level of 0.5 µg/L. SYR 2 (1998-2005) data showed 650 systems or 1.289% of 50,446 systems had detects greater than 0.5 µg/L… Only 57 (0.113%) systems had detects of CCl4 greater than the MCL of 5 µg/L." • In monitoring of public water systems, the USGS detected CCl4 in source water and finished water at levels above the PHG. • The 2019 Update of the Environmental Working Group (EWG) Tap Water Database reports that CCl4 was detected in drinking water of 256 water suppliers in 34 states, serving a total population of 3.1 million people, and that 167 drinking water utilities serving 1.1 million people had CCl4 concentrations above the California PHG. • The ATSDR notes that some studies show drinking water concentrations well above the MCL (*i.e.*, at	

	16 and 29 μg/L) and that "based on the STORET database, CCl4 was detectable in 12% of 8,858 ambient water samples," with a median concentration of 0.1 μg/L. • The EPA drinking water program has not conducted an assessment of cancer and noncancer risk from CCl4-contaminated drinking water based on current science and has no plans to do so despite extensive evidence that CCl4 levels in drinking water exceed EPA's threshold for acceptable cancer risk. EPA's exclusion of drinking water from its TSCA evaluation creates a serious and unjustified gap in health protection of exactly the type Congress intended for TSCA to address.	
45	**PUBLIC COMMENTS:** The ACC agrees that existing EPA regulatory programs addressing environmental media pathways (air, water, land) can and do adequately assess and manage exposures to these media. EPA has deviated from this assessment by choosing to address the ambient water pathway despite the existence of CWA regulations. EPA's consideration of the ambient water pathway did not uncover unreasonable risk, nor did it even produce recommendations to other program offices to pursue additional regulation under the statutes for which they have jurisdiction. Is OPPT's attempt to address environmental pathways that are already subject to significant EPA regulation under other environmental statutes in these draft TSCA risk evaluations a good use of EPA's resources? To address TSCA Section 9 and transparency concerns,	Clarifying language on exposure pathways and risks under the jurisdiction of other EPA-administered statutes have been added to section 1.4.3 of the final risk evaluation document. General population exposures from the ambient water pathway are excluded from the scope of the risk evaluation based on coverage under CWA section 304(a) and implementing regulations. OPPT worked closely with other EPA program offices during the course of the risk evaluation process and will continue to engage intra-agency coordination for future TSCA risk evaluations. This is consistent with TSCA section 9(b)(1), which directs EPA to "coordinate actions taken under [TSCA] with actions taken under other Federal laws administered in whole or in part by the Administrator."

	ACC recommends that EPA should seek: (a) for OPPT to better understand the regulatory requirements and processes of the various environmental statutes under EPA's purview; (b) for OPPT to reach agreement with the other program offices on what criteria should drive the use of TSCA risk evaluations to address air, water, and other waste pathways under the conditions of use of a TSCA high priority chemical; (c) for other program offices to understand the potential value of TSCA risk evaluations to these other EPA programs; and (d) to establish better approaches for coordinating what each program office (including EPA OPPT) can provide the others to improve environmental protection under their respective statutory authorities more efficiently and without duplication. TSCA was never intended to replace regulation by other EPA environmental programs, each of which has different requirements and standards and approaches for regulatory decision-making.	The purpose of risk evaluation under TSCA is to determine whether a chemical substance presents an unreasonable risk to health or the environment, under TSCA conditions of use. Clarifying language on exposure pathways and risks under the jurisdiction of other EPA-administered statutes have been added to section 1.4.3 of the final risk evaluation document.
Impacts of CCl4 on climate change		
23, 30, 32, 43	**PUBLIC COMMENTS:** CCl4 has a significant global warming potential (GWP), which makes it 1,730 times more potent than carbon dioxide (CO2). Assuming U.S. emissions of CCl4 are nearly 9 million pounds per year as estimated by SPARC, CO2 equivalent emissions would be 6.9 million metric tons. This amount is higher than the CO2 emissions of most coal-fired power plants and equals the annual CO2 emissions from over 1.5 million cars. The well-known consequences of global warming include far-reaching impacts on human health and the environment that should be addressed in a comprehensive risk evaluation. Yet there is no mention of CCl4's GWP in the draft evaluation, let	Clarified the following after Table 1-2 in the final risk evaluation document: "Carbon tetrachloride had several uses in the past, primarily as a feedstock for the production of chlorofluorocarbons. Current uses are now confined by the Montreal Protocol to be in contained processes. Sherry et al. (2018) reported global industrial production of carbon tetrachloride in 2014 was consumed in: (i) incineration (29 Gg); (ii) as a perchloroethylene feedstock (64 Gg); (iii) as hydrofluorocarbon feedstock (58 Gg); in (iv) methyl chloride production (26Gg); (v) in divinyl acid chloride production (23 Gg); and (vi) for use as process agents and laboratory

	alone any analysis of the significance of its emissions in contributing to climate change.	purposes (3 Gg). Sherry et al. (2018) estimated 13 Gg year^{-1} of global emissions from unreported non-feedstock emissions from chloromethane and perchloroethylene plants as the key carbon tetrachloride source. Additionally, 2 Gg year^{-1} are estimated as fugitive emissions from the usage of carbon tetrachloride as feedstock and possibly up to 10 Gg year^{-1} from legacy emissions and chlor-alkali plants."
Impacts of CCl4 on stratospheric ozone		
SACC, 23, 28, 30, 32, 43	**SACC COMMENTS:** The impact of CCl4 as an ODS in the stratosphere should be further discussed. • The draft risk evaluation indicates that CCl4 is released into the atmosphere and rapidly degrades in the stratosphere (p. 137, line 4437). • However, EPA verbally presented that CCl4 is very stable in the troposphere and that the movement to the stratosphere is an extremely slow process and is unlikely to significantly reduce tropospheric concentrations over the short term. This was supported by information in the problem formulation indicating an extremely long half-life in the troposphere. • This contradicts statements in the draft risk evaluation stating that CCl4 diffusion into the stratosphere is an important removal mechanism. Recommendation: Add more discussion on the impact of more atmospheric input and long tropospheric half-lives on ozone depletion. One Committee member cited the SPARC report on CCl4 as a source for more information on impacts. **PUBLIC COMMENTS:** • CCl4 is a significant contributor to ozone depletion, accounting for about 12% of the globally averaged chlorine and bromine in the stratosphere, compared to	Assessing ozone depletion is out of scope for this Risk Evaluation. EPA did not include the emission pathways to ambient air from commercial and industrial stationary sources, because stationary source releases of carbon tetrachloride to ambient air are under the jurisdiction of Section 112 of the CAA. Resulting exposure were out of scope as described in section 1.4.3 of the final risk evaluation for carbon tetrachloride. Carbon tetrachloride is regulated under the CAA as a Hazardous Air Pollutant (HAP) and an ozone depleting substance (CAA Sections 112 and 604). HAP provisions already account for ozone depletion and climate change in accordance with Montreal Protocol. See additional language in Section 2.1.2 of the final risk evaluation: "Carbon tetrachloride shows minimal susceptibility to indirect photolysis by hydroxyl radicals in the troposphere, where its estimated tropospheric half-life exceeds 330 years. Ultimately, carbon tetrachloride diffuses upward into the stratosphere where it is photodegraded to form the trichloromethyl radical and chlorine atoms (OECD, 2011). Carbon tetrachloride is efficiently degraded by direct

	14% for CFC-12 in 2012. CCl4 has an ozone depletion potential (ODP) of 0.82, which makes it nearly as potent as several of the CFCs. • CCl4 is a Class I ODS under the 1987 Montreal Protocol (MP) and is subject to the stratospheric ozone protection provisions of Title VI of the CAA. • Feedstock and process agent uses are considered 'nondispersive' by the MP and CAA. CCl4 continues to be legally produced and used under the CAA for 'non-dispersive' uses as feedstocks, despite evidence that chemical manufacturing and feedstock use is dispersive. • In spite of the MP controls, "there are large ongoing emissions of [CCl4] into the atmosphere." According to SPARC, "atmospheric levels of [CCl4] are currently declining at a rate slightly faster than 1% per year," 2-3 times slower than would be expected in the absence of significant emissions. • Global emissions of CCl4 are substantial when compared with other ODSs, accounting for 11-17% of all ozone depletion-weighted emissions.	photolysis under stratospheric conditions and the DT_{50} (Dissipation Time for 50% of the compound to dissipate) value is in the order of minutes. However, the troposphere to the stratosphere migration of carbon tetrachloride is very long and this migration time limits the dissipation. The rate of photodegradation increases at altitudes >20 km and beyond."

Environmental Hazard and Risk Characterization		
Charge Question 2.1: Please comment on whether the information presented supports the hazard and risk findings in the draft environmental hazard section (Section 3.1) and draft risk characterization section (Section 4.1).		
#	**Summary of Comments for Specific Issues Related to Charge Question 2**	**EPA/OPPT Response**

Selection of species for inclusion in risk evaluation		
SACC, 30, 43, 45	**SACC COMMENTS:** Recommendation: Include an evaluation of risk for terrestrial receptors or provide convincing logic why risk to terrestrial receptors would be negligible. • Terrestrial receptors should have been assessed given the large amount of waste disposed in this manner. Terrestrial organisms are briefly mentioned but were excluded from evaluation since they were considered to be covered under other EPA programs. Some Committee members expressed concern that the rationale for ignoring pathways for terrestrial organisms was cursory. Is it the existence of the other environmental regulatory statutes or the stated adequacy of those programs in addressing these pathways that justify the exclusion? If it were demonstrated that the other environmental statutes administered by EPA do not adequately assess or effectively manage these specific exposures, would terrestrial species exposure pathways then be covered under TSCA? • EPA could provide more information on how other EPA statutes are relevant to those hazards, perhaps in a flowchart. • The Agency should cite the specific documents that have examined terrestrial exposures and associated risks from CCl4. **PUBLIC COMMENTS:** • EPA did not consider any environmental release data or any data on toxicity to terrestrial or sediment-dwelling species. Other governments have classified CCl4 as "ecotoxic to terrestrial vertebrates" and the draft risk evaluation acknowledges that "terrestrial species	As explained in section 2.5.3.2 of the problem formulation (U.S. EPA, 2018b), exposure to terrestrial organisms was removed from the scope of the evaluation. However, in the final risk evaluation, EPA qualitatively evaluated the soil and land-applied biosolid pathways leading to exposure to terrestrial organisms. Exposures to terrestrial organisms from air were considered out of scope due to its coverage under the jurisdiction of the Clean Air Act. Section 1.4.3 in the final risk evaluation contains information on EPA administered regulatory programs and statutes with jurisdiction over exposure pathways to terrestrial ecological receptors from carbon tetrachloride emissions. With respect to sediment-dwelling aquatic species, carbon tetrachloride is not expected to partition to or be retained in sediment and is expected to remain in aqueous phase due to its water solubility (793 mg/L) and low partitioning to organic matter (log K_{OC} = 0.79 – 1.93 in aquifer sediments and 1.67 in marine and estuary sediments) (see section 2.1). According to the reasonably available information, carbon tetrachloride is likely to be in pore water and not adsorbed to the sediment organic matter. Thus, qualitatively, sediment-bound carbon tetrachloride exposure concentrations are expected to be low. EPA also added a quantitative assessment of exposure to sediment-dwelling aquatic organisms, which is available in Table 4-2 and Section 4.1.3 in the final risk evaluation. Briefly, the COCs were calculated based on toxicity information available in one study conducted on *Chironomus tentans* (Lee et al., 2006), and were based on body dry weight, and an AF of 5 for the acute COC, and an ACR of 10

	populations living near industrial/ commercial facilities … may be exposed via multiple routes such as ingestion of surface waters and inhalation of outdoor air." We believe this exclusion is unjustified under TSCA, which requires a comprehensive assessment of risks to the environment, and recommend that EPA revise the evaluation to address hazards and exposures to terrestrial organisms and make a risk determination for these organisms. • For sediment-dwelling species, EPA writes that "CCl4 is not expected to partition to or be retained in sediment and is expected to remain in aqueous phase due to its water solubility and low partitioning to organic matter." However, CCl4 has been detected in sediment throughout the United States, including at more than 20 federal Superfund sites. Because EPA does not measure or estimate the levels of CCl4 in that sediment or compare it to concentrations of concern for sediment-dwelling organisms, it cannot determine whether the risks to those organisms are unreasonable. • EPA OPPT decided to update its analysis of releases of CCl4 to surface waters and resulting concentrations of CCl4, based on "additional data" about ecological hazards that came to the Agency's attention after completing the CCl4 problem formulation. EPA has not explained what "additional data" drove this decision and what role the EPA Office of Water played in OPPT's reaching this decision. The mere absence of an EPA-developed water quality criteria on aquatic life (or human health) should not in and of itself trigger OPPT to include ambient water pathways in TSCA risk	for chronic COC. Because only one study was available for sediment dwelling organisms, EPA also generated acute and chronic COCs using aquatic invertebrates (*e.g.*, *Gammarus pseudolimnaeus* and *Daphnia magna*) as a surrogate species to provide an additional line of evidence to estimate toxicity to sediment-dwelling organisms in the final risk evaluation. Based on the COCs generated both from (Lee et al., 2006) and from the use of aquatic invertebrates as a surrogate, risk to sediment dwelling organisms was not indicated for acute (RQs < 1) or chronic exposures to carbon tetrachloride (RQ < 1 or RQ > 1 and less than 20 days of exceedance). As a result of a screening-level comparison of the reasonably available environmental aquatic hazard data with aquatic exposure concentrations, it was determined that no further hazard analyses were necessary (see section 2.5.3.1. of the problem formulation document) (U.S. EPA, 2018b). Upon further evaluation of the reasonably available hazard data of carbon tetrachloride after the problem formulation phase, EPA decreased the environmental hazard chronic COC from 7 µg/L to 3 µg/L. Consequently, EPA assessed the risk of aquatic organisms in the risk evaluation. The derived acute COC (90 µg/L) and chronic COC (3 µg/L) are based on environmental toxicity endpoint values (*e.g.*, EC_{50}) from Brack and Rottler (Brack and Rottler, 1994) and (Black et al., 1982; Birge et al., 1980), respectively. The data were based on high quality studies and represent the lowest bound of carbon tetrachloride data available in the public domain. Further details about the environmental hazards of carbon tetrachloride are available in Table 3-1.

	evaluations.	
Chronic ecological COC		
SACC, 45	**SACC COMMENTS:** It was unclear why the COC was changed from 7 to 3 µg/L. The calculations based on amphibians and algae are included in Table G.6 of the draft risk evaluation. Recommendation: Justify the change in COC for environmental risk from 7 to 3 µg/L. **PUBLIC COMMENTS:** EPA decreased the environmental hazard chronic COC from 7 to 3 µg/L. For clarity, EPA should reproduce the process for developing the COCs from the problem formulation document and discuss why the value was changed from 7 to 3 µg/L. Further, a summary table of the results used to calculate the COCs should be provided in this section, rather than leaving the reader to recreate it from Appendix G.	The chronic COC was initially determined to be 7 µg/L as a result of a screening-level comparison of the reasonably available environmental hazard data (see section 2.5.3.1. of the problem formulation document) (U.S. EPA, 2018b). Upon further evaluation of the reasonably available hazard data of carbon tetrachloride after the problem formulation phase, EPA decreased the environmental hazard chronic COC from 7 µg/L to 3 µg/L. Consequently, EPA assessed the risk of aquatic organisms in this draft risk evaluation. The derived acute COC (90 µg/L) and chronic COC (3 µg/L) are based on environmental toxicity endpoint values (*e.g.*, EC_{50}) from Brack and Rottler (Brack and Rottler, 1994) and (Black et al., 1982; Birge et al., 1980), respectively. The data represent the lowest bound of all carbon tetrachloride data available in the public domain and provide conservative hazard values. Further details about the environmental hazards of carbon tetrachloride are available in Table 3-1. EPA used hazard data from the most sensitive species to estimate lethality and overall effects to aquatic organisms. The chronic COC, 0.003 mg/L, was based on the LC_{10} for the European common frog (*Rana temporaria).* The COC for algae, 0.007 mg/L, was calculated separately, and was based on the EC_{10} for green algae (*Chlamydomonas reinhardtii).* EPA used an AF of 10 for the chronic and algal COC calculations to account for species that may be more sensitive but were not represented in the available data. EPA used the lowest LC_{10} (0.03 mg/L, chosen from LC_{10}s from four amphibian species ranging from 0.025 to 0.436

		mg/L) to calculate the chronic COC because, as both Birge, et al. (1980) and Black et al., (1982) noted, it delineates the concentration at which substantial reproductive impairment could occur, resulting in population-level effects. EPA incorporated this suggestion. The summary table of aquatic toxicity studies and hazard ranges used to determine the COCs has been moved into the environmental hazard section in the main document (Table 3-1).
SACC	**SACC COMMENTS:** • The Committee suggested the use of LD10 for chronic exposures, even when using an AF of 10 would be insufficient to be protective of amphibian populations. The assumption that the larval life stage is particularly sensitive may not be accurate (Appendix G, p. 272, line 7023). Studies have shown that metamorphosis can be a more sensitive life stage for some compounds (*e.g.*, thyroid disrupting substances; Johnson et al., 2017). Recommendation: Consider using benchmark dose (BMD) methods to determine a POD for amphibians and either defend the application of the AF of 10, or use an AF of 100 from the LC10, which is considered in many publications to be protective of lethal effects in aquatic organisms (Kienzler et al., 2017). Alternatively, EPA should consider using an AF of 100 instead of 10, which would incorporate additional uncertainty into risk characterization for developmental effects.	Development and metamorphosis are both sensitive endpoints for amphibians, and EPA acknowledges uncertainty due to lack of data encompassing amphibian metamorphosis. However, metamorphosis is not anticipated to be a more sensitive life stage than early amphibian development. While amphibians can be particularly vulnerable to thyroid endocrine disruption at low concentrations during metamorphosis, EPA does not have evidence that carbon tetrachloride is a thyroid endocrine disruptor. EPA is also considering (Johnson et al., 2017) in an ongoing analysis examining amphibian variation in sensitivity to inform the use of amphibian data in future risk assessment (described below). EPA examined whether BMD modeling could be applied to the toxicity data from Birge, et al. (1980) and Black et al., (1982) used to derive the acute and chronic concentrations of concern using the EPA peer reviewed BMDS (https://www.epa.gov/bmds/about-benchmark-dose-software-bmds). This methodology has been added to the Appendix. In brief, because the BMDS requires a measure of error (STD/STE) for model calculation, EPA was not able to apply these methods with the data provided by the Birge, et al.

		(1980) and Black et al., (1982) papers. However, EPA has high confidence in the toxicity values provided by both papers because the study authors applied an appropriate modeling technique (log-probit analysis) to generate LC10 and LC50 POD estimates for fish and amphibian species. EPA used OPPT methodology as cited in the risk evaluation (U.S. EPA, 2013, 2012b) and applied an AF of 10 for chronic data. EPA is considering the Keinzler et al. (2017) study, referred to by the SACC, in its assessment. EPA has developed a data driven approach to deriving AFs for a case study with amphibian data relevant to the carbon tetrachloride risk evaluation and results are summarized below: Because amphibian species are typically under-represented in chemical risk assessments relative to other taxonomic groups, little is known about the amount of variation observed across amphibian species. EPA tested whether an AF of 10, typically applied to the lowest chronic toxicity value for fish, daphnia, and algae to account for species-level variation in sensitivity, is protective of amphibians. Single chemical toxicity effects for growth, development, or mortality specific to amphibian larva were obtained from EPA's ECOTOX knowledgebase. Chemicals were characterized as having specific-acting or narcotic MOAs as predicted from chemotype (ToxPrints) and bioassay activity (ToxCast and Tox21 hits) features, and species sensitivity distributions (SSDs) were used to characterize variation in sensitivity. Based on the available data, which included 1071 EC_{50} and LC_{50} endpoints spanning 202 chemicals and 41 amphibian species, an AF of 10 was protective of 95% of the amphibian species, on average, when toxicity data for at least 5 and 10 species were available for

		narcotic and specific-acting chemicals, respectively. For carbon tetrachloride, this suggests that the AF of 10 that EPA applied to the lowest 9-day LC_{50} chosen from 7 amphibian species to calculate the acute COC, could be protective of amphibians, as they are currently represented within the ECOTOX database. For chronic exposures, the paucity of long-term data for amphibians and other taxonomic groups will make it difficult to generate data-derived AFs. However, for amphibians, short exposures during development and metamorphosis can produce effects that are relevant through the lifespan of an organism (*e.g.*, developmental abnormalities that affect growth and reproduction later in life). Initial analysis based on metamorphic and developmental endpoints, but without longer exposure chronic data, suggests that a larger AF could be warranted to generate a chronic COC that is protective of amphibians for carbon tetrachloride. However, EPA is still in the process of evaluating the body of available literature data to determine whether to revise standards for application of AFs under TSCA.
30	**PUBLIC COMMENTS:** The EPN is inclined to accept the approach used in the 2020 EPA draft for assessing CCl4 risk to algae. This view recognizes that 72- or 96-hour algal testing can be appropriately described as both an acute and a chronic exposure to a test substance because exposure takes place in a relatively short duration, but it also occurs during the reproduction of populations of individual algal cells, and it's those developing and changing cell populations that are measured. The fairly well-defined and easily measured endpoint of death in individual organisms (*e.g.*, fish) is quite different from the measuring of inhibition of growth	The approach is carried through in the final risk evaluation.

	in large populations of photosynthetic algal cells. Those endpoints are clearly quite different.	
Ecological risk characterization/interpretation		
SACC	**SACC COMMENTS:** • Overall, the information presented did not support the conclusions that expected environmental concentrations were below hazard thresholds for aquatic species. • EPA did not use conservative values to assess either exposure or hazard threshold for aquatic species. • Mean values for exposures were compared to rounded values of higher concentration threshold and did not include adequate safety factors given the uncertainty of the estimates. Recommendation: The Agency should evaluate degradation products of CCl4 and conduct risk evaluations in terrestrial organisms as well as aquatic and endangered species.	In the absence of chronic amphibian studies, EPA viewed the amphibian study 4-days post-hatch (8-9 days total) as sub-chronic and applied an AF of 10 to derive a chronic hazard value per current OPPT methodology (U.S. EPA, 2013, 2012b). EPA chose the most conservative hazard values from data available in the public domain to calculate acute and chronic COCs relevant to aquatic ecosystems. In addition, an AF of 10 was applied to the most conservative acute and chronic hazard values to account for species that may be more sensitive but were not represented in the available data. This AF was higher than the factor of 5 normally used to calculate acute COCs for aquatic invertebrates and fish, because EPA wanted to incorporate the added uncertainty around amphibians into the COC. The amphibian chronic COC of 0.003 mg/L used in this risk evaluation is two orders of magnitude more protective than if the chronic COC were derived from fish (0.2 mg/L), and more protective than if the chronic COC were derived by applying an ACR of 5 to the lowest amphibian acute hazard value. The TSCA risk evaluation focuses on exposures to particular species and environmental receptors, and appropriately considered impacts to affected species. During problem formulation, terrestrial species exposure pathways were determined to be covered under other

		environmental statues administered by EPA (*e.g.*, RCRA and CAA). However, in the final risk evaluation exposure to terrestrial organisms from the soils and biosolids pathway was evaluated qualitatively. Clarifying language about what pathways are addressed under the jurisdiction of other EPA-administered statutes has been added to Section 1.4.3 of the Risk Evaluation.
SACC	**SACC COMMENTS:** • A similar argument for additional safety factors can be made for the acute COC of 7 µg/L in fish. Table G-1 in the Evaluation clearly shows the MOA (hepatoxicity) of carbon tetrachloride was consistent between fish and mammals. The liver serves an important role in fish reproduction. Consequently, since it appears to be a target organ in fish as well as rodents, the WOE indicates reproduction may also be impaired and indicates additional uncertainty for the risk characterization statement of "no unreasonable risk."	Amphibians were more sensitive than fish to carbon tetrachloride in acute exposure scenarios by two orders of magnitude (amphibian acute hazard value of 0.9 mg/L versus fish acute hazard value of 10.4 mg/L). Thus, they were used to generate the acute COC to assess risk to aquatic organisms (excluding algae). EPA also applied a larger AF (10 versus the traditional 5 applied to acute fish data) to allow for uncertainties in the use of amphibian data. If EPA were to use the lowest toxicity value derived for fish divided by an AF of 10 versus 5, as recommended by the SACC to account for uncertainty in MOA for fish, the acute COC would still be less conservative than the COC generated using amphibian data (1.04 mg/L versus 0.09 mg/L). The use of amphibian toxicity data yields a COC most protective of aquatic life in acute exposure scenarios.
SACC	**SACC COMMENTS:** Recommendation: A 9-day exposure value should be compared to the value of 2.5 µg/L instead of the rounded-up value of 3 µg/L. • The use of 20 days of exceedance to determine risk was based on chronic invertebrate and fish assays normally taking 21 or 28 days. However, if a developmental assay is used as a threshold of effect, days of exceedance are not a relevant comparison, as development can be altered by exposure at even hourly	After the application of an AF of 10, the chronic COC was rounded to the nearest 1 ppb. The COC was rounded from 2.5 to 3 µg/L due to lack of precision in the reported experimental data (where the LOD was 5 ppb) and uncertainty in the extrapolation of data from a few organisms to represent hazard for entire trophic levels. EPA considered the recommendation that shorter exceedance values (< 20 days) may be relevant to determine risk to aquatic organisms when hazard is derived from

	exposure durations. • The rationale to consider RQ exceedances for up to 20 days as acceptable for a lethal endpoint was not provided. *Ambystomidae*, a species of salamanders (not the species used in this draft risk evaluation, but the lifespan is expected to be similar), live for 30 years. Therefore, by definition, a chronic exposure would exceed 3 years, although only ~1 month is typically spent in any one water body. • One Committee member suggested that any time point can be used for RQ evaluations given the uncertainties of the data. If a developmental value is to be used, the designation "Non-applicable" should be placed in columns for acute days of exceedance in Tables E2 and E3 of the risk evaluation. • The risk characterization was not straightforward, and uncertainties should have been explicitly stated and an attempt should have been made to account for them.	developmental endpoints. Exposure for short durations during development can cause permanent adverse effects in vertebrates. Because, for carbon tetrachloride, the chronic COC was based on mortality observed during amphibian development in a 9-day exposure, EPA added calculations of chronic risk for amphibians where RQs were > 1 (and exceedance was 0 days or greater). This scenario was compared to the traditional assessment methodology (where chronic risk = RQ >1 and > 20 days exceedance) to provide a range that considered the biological relevance of short exposures during development. This risk calculation has been added in section 4.1.1. Although there were no data reasonably available for long lived salamander species, EPA expects the chronic COC should be protective of amphibians. EPA used the most sensitive toxicity value from a 9-day exposure during development (a sensitive life history stage), applied an AF of 10 to account for uncertainty surrounding differences across life stages and species, and added a risk bracket for conservative scenarios where RQ > 1. EPA explicitly stated uncertainties in Section 4.4.3 and accounted for them by applying AFs in its risk calculations.
SACC	**SACC COMMENTS:** There was no consideration of effects in the aquatic prey base, which were not evaluated.	Hazard data for algae and aquatic invertebrates were evaluated and were found to be less sensitive than amphibians.
SACC	**SACC COMMENTS:** • If Table 4.2 is evaluated in the light of any exceedance of the predicted E-FAST value, the occurrence of RQ >1 for 5 out of 21 sites for the 20-day exposure estimates and 4 out of 21 for the 250-day exposure estimates would indicate that a more refined risk characterization is needed, perhaps with measured	There were five facilities that indicated risk for aquatic organisms from chronic exposure to carbon tetrachloride (RQ ≥ 1 for the chronic COC based on a developmental endpoint). EPA subsequently refined the assessment to examining when released occurred at each of these five facilities to determine if amphibian development could realistically be affected.

	values in surface water. The Committee suggested these values could be obtained from the NPDES monitoring reports from the same dischargers used to estimate surface water values. Recommendation: If the RQ is >1 in multiple sites, a more refined risk characterization with better uncertainty estimates is needed.	Timing of exposure is important to consider because amphibian development is constrained seasonally throughout the U.S., and typically spans only 2-4 months out of any given year. Where releases occurred and data were available, EPA calculated surface water concentrations using E-FAST and associated, site-specific RQs to determine whether risk was or was not indicated at the facilities during these key time periods. Risk was not indicated during time periods relevant to amphibian development at Eco Services Operations Facility (RQs< 1 for the three years where monitoring information was available). At the other four facilities, risk was indicated (RQs > 1) during the time periods relevant to amphibian development for at least 2 separate reporting periods. However, risk was not consistent or predictable across years or facilities (*e.g.*, some years no releases of carbon tetrachloride occurred, or RQs < 1). This refined analysis has been added to section 4.1.2 and in Appendix (Table F-2).
SACC	**SACC COMMENTS:** Recommendation: Specifically note the criteria used to assess data relevance for risk assessment in addition to determining data quality and consider using other data (including those not considered high quality) in a corroborative sense to support high-quality studies used to develop a COC. A simple flow chart on this process may help clarify these issues in the risk evaluation. • In the methodology presented in Section 3.1.1, it is not clear how the ECOTOX database was used. • There is a lot of information presented in Appendix G that would have been clearer if included in the body of the draft risk evaluation. In Table G-1, many studies conducted in fish evaluated enzyme induction (which is not in itself an adverse effect) and some are	Relevance was iteratively assessed throughout the systematic review process, from data search to data integration. In all evaluation strategies, professional judgment is employed to determine the adequacy or appropriateness of the qualitative rating assigned by the numerical scoring system. As discussed in the *Application of Systematic Review in TSCA Risk Evaluations*, OPPT leveraged EPA's ECOTOXicology knowledgebase (ECOTOX) as a source of single chemical toxicity data for aquatic and terrestrial organisms. Using a modified ECOTOX literature search and screening protocol, OPPT performed a wide search based on chemical-specific search terms to gather ecological toxicity information. Title/abstract and full-text screening decisions were based on the modified ECOTOX minimum applicability

	intraperitoneal exposures that were judged to be high in data quality. The draft risk evaluation (p. 96, lines 3072-3073) states that 61 of the 73 studies were of unacceptable data quality (suggesting that they were excluded); however, Table G-1 has more than 12 studies that are rated high in quality. Therefore, it seems that EPA used other criteria to determine acceptability in addition to data quality. This was also inferred in lines 6992-7003. These criteria could be added to the table as an additional column. Consider highlighting what studies were selected and used.	criteria that parsed citations into "on-topic" and "off-topic" bins. The "on-topic" references were further subjected to a full-text screening step to confirm relevancy. Only citations that fulfilled the full-text screening criteria moved to the data evaluation step. The data quality extraction results for carbon tetrachloride environmental hazard are presented in Appendix Table F-1. This table contains citations considered as on-topic according to the ECOTOX criteria but some of these citations were excluded from further consideration due to their unacceptable data quality based on pre-defined data quality evaluation criteria in the *Application of Systematic Review in TSCA Risk Evaluations* and/or were deemed out of scope. For example, certain environmental studies on carbon tetrachloride were of high quality but were not biologically relevant for purposes of environmental hazard assessment due to the reported endpoints (*e.g.*, glutamic pyruvic transaminase activity, serum total protein, catalase activity, sodium concentration in blood, whole body residue). These studies (Chen et al., 2004); (de Vera and Pocsidio, 1998); (Barrows et al., 1980); (Liu et al., 2015); (Jia et al., 2013); (Kotsanis and Metcalfe, 1988); (Weber et al., 1979); (Koskinen et al., 2004); (Bauder et al., 2005); (Martins et al., 2007)) are contained within the on-topic data evaluation section of Appendix F.1, but were not used within the risk evaluation process. During risk evaluation, EPA made refinements to the conceptual models resulting in the elimination of the terrestrial exposure pathway and studies that are not biologically relevant from further analysis. In the final risk evaluation, exposures to terrestrial organisms from biosolids and soils were evaluated qualitatively based on physical-

		chemical properties. EPA/OPPT's quality evaluation method was developed following identification and review of various published qualitative and quantitative scoring systems to inform EPA/OPPT's fit-for-purpose tool. The development process involved reviewing various evaluation tools/frameworks (*e.g.*, OHAT Risk of Bias tool, CRED, etc.; see Table 1 and Appendix A of the *Application of Systematic Review in TSCA Risk Evaluations* document and references therein), as well as soliciting input from scientists based on their expert knowledge about evaluating various data/information sources for risk assessment purposes. In order to ascertain the quality of the available data, EPA is using a numerical scoring system to assign a qualitative rating. This approach adds consistency and transparency to the evaluation process. Scores will be used for the purpose of assigning the confidence level rating of High, Medium, Low, or Unacceptable, and inform the characterization of data/information sources during the data integration phase. Of the 75 on-topic environmental hazard sources identified by the ECOTOX process, 60 citations were considered out of scope and/or unacceptable in data quality based on the data quality evaluation metrics and the rating criteria described in the *Application of Systematic Review in TSCA Risk Evaluations*. The data quality evaluation results for the remaining 15 on-topic studies for carbon tetrachloride environmental hazard are presented in the document Risk Evaluation for Carbon Tetrachloride, Systematic Review Supplemental File: Data Quality Evaluation of Environmental Hazard Studies (U.S. EPA, 2019).

		EPA has incorporated the feedback from SACC for inclusion of more environmental hazard information in the body of the risk evaluation document. The summary table of relevant aquatic toxicity data used to determine the COCs from the Appendix F-2 Hazard Identification – Aquatic Section into the environmental hazard section in the main document (Table 3-1). Refinements to the evaluation strategies are likely to occur. EPA already made changes to the physical chemical properties, environmental hazard, and epidemiological criteria since the *Application of Systematic Review in TSCA Risk Evaluations* was published. These changes were due to validation and improvement efforts to ensure that the most relevant studies were included in the TSCA risk evaluations, and the most up-to-date data quality evaluation criteria will be available for review in the upcoming the *Systematic Review Protocol Supporting the TSCA Risk Evaluations* document (under development). The TSCA evaluation strategies consider methodological design and implementation and reporting within the existing domains and metrics. Since it is difficult to have high confidence in data where the underlying methods that are unreported or poorly reported, EPA assesses reporting and methodological quality simultaneously. However, EPA recognizes the challenge of discerning between a deficit in reporting and a problem in the underlying methodological quality of the data/information source. Developing a reporting checklist, guidance document or a separate reporting quality domain may be possible in the future as EPA uses and optimizes the evaluation strategies.

SACC	**SACC COMMENTS:** Recommendation: Describe why more robust methods (*e.g.*, species sensitivity distributions) could not be used for the identification of environmental hazards.	EPA explored the use of robust statistical methodologies including species sensitivity distributions (SSDs) and BMD modeling as additional lines of evidence for how carbon tetrachloride exposure could affect the most sensitive taxonomic group, amphibians. This information has been added to the Appendix F of the final risk evaluation. EPA generated SSDs using the SSD Toolbox, a resource created by EPA's Office of Research and Development (ORD) (Etterson, 2019). There was insufficient data (n = 4 species) to examine the LC10 data for amphibians using an SSD. There was enough data (n = 7 species) to preliminarily examine LC_{50} data from the 4-days post-hatch exposure. Using the three best-fitting distributions, the model averaged HC5 (the hazardous concentration intended to be protective of 95% of amphibians) was = 0.42 mg/L (+/- 0.36 SE). This value is within range of EPA's COC of 0.09 mg/L (the most sensitive amphibian LC50 0.9 mg/L, divided by an Assessment Factor of 10). Although 7 species are not enough to represent the total variation in sensitivity across the amphibian taxa, the SSD did reveal that the model frog Xenopus laevis appeared to be less sensitive than other species (Figure 1). The American bullfrog (*Rana catesbiana*) and the European common frog (*Rana temporaria*) were the most sensitive species in the dataset (Figure 1). The SSD provided a useful line of evidence that EPA used to visually assess the distribution of the available amphibian toxicity data. However, due to the collective uncertainties including unknown total variation in amphibian sensitivity, a small sample size (n = 7 species, from two studies), and possible differences across amphibian life stages, EPA used the more

		conservative COC generated by dividing the lowest hazard value by an AF of 10 to assess risk due to acute exposure.
SACC	**SACC COMMENTS:** Recommendation: RQs should be made on conservative data from exposures as well as effects. • The aqueous exposure estimates in Tables E-2 and E-3 of the draft risk evaluation are not conservative because mean and median values were used. A more conservative value would be the maximum value or at least a 90th percentile value, if available from the model. Several Committee members wondered if the later data from NPDES permits agreed or disagreed with the TRI data. • The acute and chronic stream concentrations reported in Table E-2 were computed in E-FAST using 5-year mean releases from Table E-1. The mean average reported in this analysis should include a value other than zero for early years when the facility was not manufacturing or using CCl4. It should be clearly indicated that the facility was up and running and using/producing CCl4 for each of these years. • Seven sites show releases only for 2018, the last year of data. For these sites, the best estimate of average release is 5X the value presented in Table E-1. • Increases in releases were apparent for three sites. A more reasonable estimate of mean releases for increasing sites might be to extrapolate releases for the next 6 years (timeframe for SDWA review) and use the average of these values in E-FAST. The existence of an upward trend in releases should be examined for all 49 sites reporting releases. • The other (default) input values to the E-FAST model for each of the top release sites are not reported.	The aqueous exposure estimates presented in the final risk evaluation were based on E-FAST modeling of surface water carbon tetrachloride concentrations. The E-FAST model used the conservative, hydrologically-based 7Q10 design flow statistic (average 7 consecutive day of lowest flow occuring once every 10 years). The 7Q10 is used by EPA and states for water quality standards, to estimate toxic wasteload allocation, and permitted discharge limits in NPDES permits. For the final risk evaluation, EPA also analyzed carbon tetrachloride discharges from 5 facilities during biologically sensitive times of year (*e.g.*, spring and summer) and found that 90th percentile discharges do not occur during any given month from these facilities. Given the variability in carbon tetrachloride discharges for any given year, EPA averaged facilities' discharges over a five-year period (2014-2018). EPA added a footnote to clarify averaging to include zero discharges. Though it appears that some facilities' releases are increasing, EPA did not extrapolate releases, instead based the surface water concentration estimates on the 5-year releases since this characterizes the variability in discharges over time. A review of 2019 carbon tetrachloride releases confirms this assumption, as compared to 2018 levels, releases in 2019 decreased to levels similar to those in 2017. EPA has added text in Section 2.3 to list all inputs used in E-FAST modeling.

	• The analysis in Appendix E tends to focus on the top 21 release sites, but there are only 49 TRI reporting facilities. The Committee indicated that conducting the analysis on all 49 sites is not much greater than the effort for the 21 sites; hence, all 49 sites should be reported and evaluated.	TRI and DMR data are both facility reported EPA data but since each has different reporting requirements, comparison between the two is not always applicable. EPA has added a chart in Appendix E to present the carbon tetrachloride release trends from all discharging facilities for each of the five years (2014-2018) as listed in EPA's DMR database.
SACC	**SACC COMMENTS:** Recommendation: Include CCl4 transformation products in the risk evaluation. • The toxicity for major CCl4 transformation products, such as $CHCl_3$, should be considered. This is essential given EPA's reliance on degradation to remove CCl4 from water and sediment.	Reasonably available toxicity information was used to assess the toxicity of carbon tetrachloride to aquatic and sediment organisms. Information on carbon tetrachloride's fate is used within other EPA administered regulations (*i.e.*, CWA, CAA) to determine the safety of measures for carbon tetrachloride and its transformation products in environmental media. Section 1.4.3 of the final risk evaluation provides information on exposure pathways and risks addressed by other EPA administered statutes.
SACC	**SACC COMMENTS:** Recommendation: Discuss the possible impact on endangered species. • The E-FAST model demonstrated that there is a feature that allows "searching for endangered species in the vicinity of specific facilities," which may be useful to production and use decisions where they are present.	The TSCA risk evaluation focuses on exposures to particular species and environmental receptors, and appropriately considered impacts to affected species.
SACC	**SACC COMMENTS:** Recommendation: EPA should be very specific in language describing risks based on what was and was not assessed. Broad statements of "no risk" are misleading given that all risks are relative and no condition where exposure is present is without some level of risk. The environmental risk characterization should be qualified to the organisms actually evaluated and the conclusion of no unreasonable risk based on environmental concentrations above hazard thresholds be reconsidered.	EPA has added clarifying language in the risk characterization section 4.1. While some site-specific RQs, calculated from modeled release data from particular facilities, are greater than or equal to 1, indicating risk, uncertainties related to these particular estimates (discussed specifically in section 4.1) of the risk evaluation support a determination of no unreasonable risk for the environment (section 5.2.2).

	• There may be risks to environmental receptors that are not assessed in this draft risk evaluation. Only aquatic receptors were evaluated and there is a reasonable probability that their exposures are underestimated. The text points out uncertainties that may overestimate risk, but it is also possible that these uncertainties could lead to underestimation. • The language used to describe the scope of this assessment is insufficient. The limitation to only the aquatic species and confinement to releases directly to water must be explicitly stated. The condition of use language obfuscates the severe limitation of this assessment. • The Committee concluded that EPA cannot state that there is no unreasonable risk to environmental organisms exposed via surface water. The environmental concentrations are above the hazard thresholds and the conclusion of no unreasonable risk is not fully justified.	
43	**PUBLIC COMMENTS:** EPA ignores unreasonable risks to algae species (four acute RQs between 6.4 and 18 and two chronic RQs above 1.0), asserting that "[d]ue to the quick regeneration time of many algae species, impacts to algae populations would be most likely over long-term consecutive days of release (*i.e.*, > 20) versus an interval or pulse exposure." • EPA provides no data on the algal regeneration times and does not consider how severe acute impacts lasting <20 days may affect that regeneration. • EPA does not justify the assumption that survival of the species is the only relevant endpoint and acute risks to algae from releases lasting <20 consecutive days are reasonable.	The risk determination for algae is based on an RQ > 1 and >20 days exceedance. The 20-day criterion is derived from partial life cycle tests (*e.g.*, daphnid chronic and fish early life stage tests) that typically range from 21 to 28 days in duration. It is also important to note that the PDM estimates the total number of days out of 1 year that the COC is exceeded, and the days are not necessarily consecutive. Thus, the day criterion is considered likely to protect algae. EPA considered algal endpoints separately from the other taxa, because durations normally considered acute for other species (*e.g.*, 48, 72, or 96 hours) can encompass several generations of algae. EPA also used a more sensitive hazard

	• EPA's approach eliminates the possibility of unreasonable acute risks to algae: even if a single exposure was sufficient to decimate a local algae species, EPA would not consider risk to be unreasonable unless the release were repeated for 20 consecutive days. • EPA has always considered acute algal toxicity as a relevant endpoint, and the algae COC for CCl4 was calculated based on an acute (72-hour) test. The final EPA evaluation should determine that CCl4 presents an unreasonable risk to the environment.	endpoint (EC_{10}) instead of an acute endpoint (EC_{50}) to generate a COC relevant to algae. As such, EPA's approach is protective of acute exposures to algae and is relevant to point effects beyond mortality (*e.g.*, reductions in growth, yield, etc.) that are observed to effect at most % 10 of an algae population. EPA determined that effects of carbon tetrachloride on the algae population would likely occur over long-term consecutive days of release versus an interval or pulse exposure due to its volatile properties. Therefore, EPA concludes that there is no unreasonable risk to algae from carbon tetrachloride under the conditions of use.
23, 30, 43	**PUBLIC COMMENTS:** For aquatic species, EPA calculated an acute RQ above 1.0 resulting from CCl4 releases from the Dover Chemical site in Ohio. However, EPA ignores the resulting risks because "noncompliance and spills are not in the scope of this risk evaluation." EPA does not even provide data on CCl4 releases from a Sea World facility in California because "the reported level is above permit discharge limits." In other words, EPA knows of unsafe releases of CCl4 to the environment, but it fails to consider them in the risk evaluation because it attributes them to spills or releases. This exclusion violates TSCA, which requires EPA to consider all exposures from CCl4's "intended, known or reasonably foreseen" conditions of use, including "spills, leaks, and other uncontrolled discharge[s]." The Ninth Circuit has also held that "spills, leaks, and other uncontrolled discharges ... would thus qualify as 'disposals' (and therefore conditions of use)."	Spills and leaks generally are not included within the scope of TSCA risk evaluations because in general they are not considered to be circumstances under which a chemical substance is intended, known or reasonably foreseen to be manufactured, processed, distributed, used, or disposed of. To the extent there may be potential exposure from spills and leaks, EPA is also declining to evaluate environmental exposure pathways addressed by other EPA-administered statutes and associated regulatory programs. However, EPA confirmed that there were regulatory actions outside TSCA associated with these accidental or noncompliance spills. First, EPA does not identify carbon tetrachloride spills or leaks as "conditions of use." EPA does not consider carbon tetrachloride spills or leaks to constitute circumstances under which carbon tetrachloride is manufactured, processed, distributed, used, or disposed of, within TSCA's definition of "conditions of use." Congress specifically listed discrete, routine chemical lifecycle stages within the statutory definition of "conditions of use" and EPA does not believe it

		is reasonable to interpret "circumstances" under which carbon tetrachloride is manufactured, processed, distributed, used, or disposed of to include uncommon and unconfined spills or leaks for purposes of the statutory definition. Further, EPA does not generally consider spills and leaks to constitute "disposal" of a chemical for purposes of identifying a condition of use in the conduct of a risk evaluation. In addition, even if spills or leaks of carbon tetrachloride could be considered part of the listed lifecycle stages of carbon tetrachloride, EPA has "determined" that spills and leaks are not circumstances under which carbon tetrachloride is intended, known or reasonably foreseen to be manufactured, processed, distributed, used, or disposed of, as provided by TSCA's definition of "conditions of use," and EPA is therefore exercising its discretionary authority under TSCA section 3(4) to exclude carbon tetrachloride spills and leaks from the scope of the carbon tetrachloride risk evaluation. The exercise of that authority is informed by EPA's experience in developing scoping documents and risk evaluations, and on various TSCA provisions indicating the intent for EPA to have some discretion on how best to address the demands associated with implementation of the full TSCA risk evaluation process. Specifically, since the publication of the Risk Evaluation Rule, EPA has gained experience by conducting ten risk evaluations and designating forty chemical substances as low- and high-priority substances. These processes have required EPA to determine whether the case-specific facts and the reasonably available information justify identifying a particular activity as a "condition of use." With the experience EPA has gained, it is better situated to

		discern circumstances that are appropriately considered to be outside the bounds of "circumstances… under which a chemical substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of" and to thereby meaningfully limit circumstances subject to evaluation. Because of the expansive and potentially boundless impacts that could result from including spills and leaks as part of the risk evaluation (*e.g.*, due to the unpredictable and irregular scenarios that would need to be accounted for, including variability in volume, frequency, and geographic location of spills and leaks; potential application across multiple exposure routes and pathways affecting myriad ecological and human receptors; and far-reaching analyses that would be needed to support assessments that account for uncertainties but are based on best available science), which could make the conduct of the risk evaluation untenable within the applicable deadlines, spills and leaks are determined not to be circumstances under which carbon tetrachloride is intended, known or reasonably foreseen to be manufactured, processed, distributed, used, or disposed of, as provided by TSCA's definition of "conditions of use." Exercising the discretion to not identify spills and leaks of carbon tetrachloride as a COU is consistent with the discretion Congress provided in a variety of provisions to manage the challenges presented in implementing TSCA risk evaluation. See *e.g.*, TSCA Sections 3(4), 3(12), 6(b)(4)(D), 6(b)(4)(F). In particular, TSCA Section 6(b)(4)(F)(iv) instructs EPA to factor into TSCA risk evaluations "the likely duration, intensity, frequency, and number of exposures under the conditions of use...," suggesting that activities for which duration, intensity, frequency, and number of exposures

		cannot be accurately predicted or calculated based on reasonably available information, including spills and leaks, were not intended to be the focus of TSCA risk evaluations. And, as noted in the preamble to the Risk Evaluation Rule, EPA believes that Congress intended there to be some reasonable limitation on TSCA risk evaluations, expressly indicated by the direction in TSCA Section 2(c) to "carry out [TSCA] in a reasonable and prudent manner." For these reasons, EPA is exercising this discretion to not consider spills and leaks of carbon tetrachloride to be COUs. Second, even if carbon tetrachloride spills or leaks could be identified as exposures from a COU in some cases, these are not forms of exposure that EPA expects to consider in the carbon tetrachloride risk evaluation. TSCA Section 6(b)(4)(D) requires EPA, in developing the scope of a risk evaluation, to identify the hazards, exposures, conditions of use, and potentially exposed or susceptible subpopulations the Agency "expects to consider" in a risk evaluation. This language suggests that EPA is not required to consider all conditions of use, hazards, or exposure pathways in risk evaluations. EPA has chosen to tailor the scope of the risk evaluation to exclude spills and leaks in order to focus analytical efforts on those exposures that present the greatest potential for risk. In the problem formulation documents for many of the first 10 chemicals undergoing risk evaluation, EPA applied the same authority and rationale to certain exposure pathways, explaining that "EPA is planning to exercise its discretion under TSCA 6(b)(4)(D) to focus its analytical efforts on exposures that are likely to present the greatest concern and consequently merit a risk evaluation under TSCA...." This

		approach is informed by the legislative history of the amended TSCA, which supports the Agency's exercise of discretion to focus the risk evaluation on areas that raise the greatest potential for risk. See June 7, 2016 Cong. Rec., S3519-S3520. In addition to TSCA Section 6(b)(4)(D), the Agency also has discretionary authority under the first sentence of TSCA Section 9(b)(1) to "coordinate actions taken under [TSCA] with actions taken under other Federal laws administered in whole or in part by the Administrator." TSCA Section 9(b)(1) provides EPA authority to coordinate actions with other EPA offices, including coordination on tailoring the scope of TSCA risk evaluations to focus on areas of greatest concern rather than exposure pathways addressed by other EPA-administered statutes and regulatory programs, which does not involve a risk determination or public interest finding under TSCA Section 9(b)(2). EPA has already tailored the scope of this risk evaluation using such discretionary authorities with respect to exposure pathways covered under the jurisdiction of other EPA-administered statutes and associated regulatory programs (see section 1.4.3). Following coordination with EPA's Office of Land and Emergency Management (OLEM), EPA has found that exposures of carbon tetrachloride from spills and leaks fall under the jurisdiction of RCRA. See 40 CFR 261.33(d) (defining in part a hazardous waste as "any residue or contaminated soil, water or other debris resulting from the cleanup of a spill into or on any land or water of any commercial chemical product or manufacturing chemical intermediate having the generic name listed [40 CFR 261.33(e) or (f)], or any residue or contaminated soil, water

		or other debris resulting from the cleanup of a spill, into or on any land or water, of any off-specification chemical product and manufacturing chemical intermediate which, if it met specifications, would have the generic name listed in [40 CFR 261.33(e) or (f)]"); 40 CFR 261.33(f) (listing carbon tetrachloride as hazardous waste no. U211). As a result, EPA believes it is both reasonable and prudent to tailor the TSCA risk evaluation for carbon tetrachloride by declining to evaluate potential exposures from spills and leaks, rather than attempt to evaluate and regulate potential exposures from spills and leaks under TSCA. Finally, EPA notes that the Ninth Circuit in SCHF v. EPA presented examples of circumstances that may qualify as disposal but did not establish a "precise meaning of 'disposal.'" 943 F.3d 397, 426 (9th Cir. 2019). The Court also did not opine on EPA's authority to determine the circumstances under which a chemical substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used or disposed of.] EPA has clarified the assessment of the Dover facility (see Section 4.1 in the Carbon Tetrachloride Risk Evaluation). In brief, EPA identified an elevated environmental release of carbon tetrachloride in 2014 at Dover Chemical in Ohio (NPDES ID OH0007269) due to an unexpected chemical spill. Because spills and leaks are not included within the scope of TSCA risk evaluations, the 2014 release was not included in the analysis. Other releases from the Dover facility, not due to the chemical spill, were evaluated. EPA has clarified Sea World carbon tetrachloride discharges. Specifically, EPA has estimated the surface water

		concentration from Sea World-specific carbon tetrachloride annual loading/releases to Mission Bay using a proxy facility in San Diego since Sea World permit data was not available in E-FAST 2014. For discharges into oceans and bays, E-FAST estimates a dilution factor of 1. EPA has revised the Carbon Tetrachloride Risk Evaluation to include a greater explanation of the E-FAST 2014 modeling approach, model calculations, inputs and results for the one year, 2014, of carbon tetrachloride releases from Sea World and the resultant surface water concentration and aquatic exposure estimates.
26	**PUBLIC COMMENTS:** For environmental risk, EPA's own analyses showed that CCl4 presents an unreasonable risk to aquatic organisms (p. 144), but EPA dismisses this unreasonable risk with little explanation: "Although the chronic COC was exceeded by four facilities ranging from 1.2 to 3.4 (*i.e.*, worst-case scenario; RQ = 3.4) and the algae COC was exceeded by four facilities ranging from 6.4 to 18 based on the 20-day stream concentration and by two facilities ranging from 1.4 to 1.5 based on the 250-day stream concentration, these CCl4 releases are not continuously released over time (*i.e.*, chronic exposure) (p. 144)." Yet for at least one of these facilities, the chronic COC was exceeded for 15 days (p. 142). It is clearly reasonably foreseeable that longer exposures may occur. Based on EPA's own analyses, EPA found risks to aquatic organisms from multiple facilities, but EPA dismissed this risk. This approach is arbitrary and capricious because EPA refuses to accept the outcomes of its own analyses, and EPA's conclusions run contrary to the evidence before the Agency. EPA should find an unreasonable risk to the environment presented by certain disposal and recycling	EPA has added clarifying language in the risk characterization section 4.1. All facilities assessed in this risk evaluation and associated RQs are presented in Table 4 2. While some site-specific RQs, calculated from modeled release data from particular facilities, are greater than or equal to 1, indicating risk, uncertainties related to these particular estimates (discussed specifically in section 4.1 and 5.2.2) of the risk evaluation support a determination of no unreasonable risk for the environment.

	conditions of use. The SACC should address EPA's unwarranted dismissal of these environmental risks.	

Occupational Exposure and Releases		
Charge Question 3.1: Please comment on the characterization of occupational exposure for workers and ONUs. Is the occupational exposure characterization supported by the information presented in Section 2.4 of the Draft Risk Evaluation? What other additional information, or approaches if any, should be considered? **Charge Question 3.2:** Please comment on the scientific validity and transparency of EPA's approach and the assumptions EPA used to characterize exposure for ONUs. Please also comment on the uncertainties related to the assumptions used to characterize exposures for ONUs. **Charge Question 3.3:** Please comment on the approaches and assumptions used and provide any specific suggestions or recommendations for alternative approaches, models or information that should be considered by the Agency for improving the workplace exposure assessment. More specifically, if other sources of monitoring data are available to estimate air concentrations for worker exposures, please provide specific citations. **Charge Question 3.4:** Please comment on assumptions used in the absence of specific exposure information (*e.g.*, dermal surface area assumptions: high-end values, which represents two full hands in contact with a liquid: 890 cm^2 (mean for females),1070 cm^2 (mean for males); central tendency values, which is half of two full hands (equivalent to one full hand) in contact with a liquid and represents only the palm-side of both hands exposed to a liquid: 445 cm^2 (females), 535 cm^2 (males)). **Charge Question 3.5**: Please comment on EPA's approach to characterizing the strengths, limitations and overall confidence for each OES presented in Section 2.4.1. Please comment on the appropriateness of these confidence ratings for each scenario. Please also comment on EPA's approach to characterizing the uncertainties summarized in Section 4.4.1.		
#	**Summary of Comments for Specific Issues Related to Charge Question 3**	**EPA/OPPT Response**
Conditions of use considered		
SACC, 23, 30, 32, 43	**SACC COMMENTS:** • The assertion of *de minimis* exposures is not adequately supported by citations or data (p. 30, lines 1062-1103). The assertion of "no use" is weakened by the admission that "CCl4 may be present in a limited number of industrial products with chlorinated ingredients at a concentration of less than 0.003% by weight," that is, 30 pounds per million pounds of	The Consumer Product Safety Commission (CPSC) banned the use of carbon tetrachloride in consumer products (excluding unavoidable residues not exceeding 10 ppm atmospheric concentration) in 1970. As a result of CPSC's ban, EPA does not consider the use of carbon tetrachloride-containing consumer products produced before 1970 to be known, intended, or reasonably foreseen. In accordance with the CPSC ban, carbon tetrachloride is not identified in the

	product, but there are millions of pounds of product created each year. Recommendation: Add discussion, citations, or data to better support the assertion of *de minimis* exposures.	California Air Resources Board consumer product database nor the Washington State Product Testing Data list or the State of Vermont list of Chemicals in Children's Products and no consumer uses are listed in the CDR.
	PUBLIC COMMENTS: In a 2017 preliminary survey of CCl4's conditions of use, EPA identified CCl4-containing products available to consumers; yet there is no discussion of manufacturing, processing, distribution, use, or disposal of these products in the draft risk evaluation. This flaw should be remedied in the final evaluation. There is no discussion of these products in the draft risk evaluation and no explanation of why the CCl4 levels they contain would be too low to pose any health concern. CCl4 is known to be released from consumer products and several products known to contain CCl4 remain in use. Sodium hypochlorite (NaOCl) and many organic chemicals contained in household cleaning products may react during use to generate CCl4. The SPARC report lists use of hypochlorite as bleach in domestic applications as a CCl4 emissions source. A 2008 study (Odabaşı, 2008) measured CCl4 concentrations of 0.25–459 μg/m3 in emissions from eight different chlorine bleach-containing household products. In a search of retail websites, SCHF identified five consumer sealant products with SDSs indicating the presence of CCl4 at levels of up to 1 percent by weight. Given the low ambient concentrations of CCl4 linked to cancer and other adverse effects, there is no basis to assume that CCl4 releases from these products would be without concern, particularly when combined with outdoor	As stated in the Problem Formulation, EPA determined after additional public outreach, literature searches and other reasonably available information, the consumer uses of carbon tetrachloride that were initially identified in the Scope document (*i.e.*, commercially available aerosol and non-aerosol adhesives/sealants, paints/coatings, and cleaning/degreasing solvent products) only have the potential for negligible exposure. Carbon tetrachloride is not a direct reactant or additive in the formulation of solvents for consumer use in cleaning and degreasing, adhesives and sealants or paints and coatings. Trace levels of carbon tetrachloride in the chlorinated substances used to manufacture the products are expected to volatilize during the product manufacturing process. No additional information was received by EPA following the publication of the problem formulation that would update the problem formulation conclusion that carbon tetrachloride is expected to be present in consumer products at trace levels resulting in *de minimis* exposures or otherwise insignificant risks and therefore that consumer uses do not warrant inclusion in the risk evaluation. EPA obtained information indicating that SDSs for industrial and commercial products manufactured with chlorinated compounds made with carbon tetrachloride as a process agent report overestimated range concentrations, and that those

	air and drinking water exposures by consumers who also use the products. EPA indicates that "direct use of CCl4 as a reactant or additive in the formulation" of consumer products is prohibited under the MP and CPSC regulations. CPSC regulations allow "manufacturing residues of CCl4 that… do not result in an atmospheric concentration of CCl4 greater than 10 parts per million." EPA maintains that this residual CCl4 is only "present in consumer products at trace levels resulting in *de minimis* exposures or otherwise insignificant risks and therefore consumer uses do not warrant inclusion in the risk evaluation." TSCA does not permit exclusion of conditions of use based on the theory that they lead to *de minimis* exposure. Further, there is no way to know if a route of exposure is *de minimis* unless it is subject to risk evaluation. The Agency has neither provided its definition or interpretation of "*de minimis*" or "insignificant risk" nor presented any criteria by which one can determine if a condition of use represents *de minimis* or insignificant risk. EPA's decision not to evaluate these exposure scenarios was thus arbitrary and unwarranted and results in a significant understatement of CCl4's human health impacts.	estimates are not based on analytical measured concentrations or on manufacturing process information. In exercising its discretion under section 6(b)(4)(D) to identify the conditions of use that EPA expects to consider in a risk evaluation, EPA believes it is important for the Agency to have the discretion to make reasonable, technically sound scoping decisions. EPA anticipates that any risks presented by the presence of carbon tetrachloride as a byproduct formed during the manufacturing, processing or use of the parent compound will be considered in the scope of the risk evaluation of the parent compound (see the executive summary of the Final Scope of the Risk Evaluation for 1,2-dichlorethane as an example: https://www.epa.gov/sites/production/files/2020-09/documents/casrn_107-06-2_12-dichloroethane_final_scope.pdf). Therefore, EPA did not evaluate hazards or exposures to consumers or bystanders to consumer use in this risk evaluation in the exercise of the Agency's discretionary scoping authority under TSCA sec. 6(b)(4)(D). See section 1.4.2.2 of the risk evaluation for more information. Risks from background concentrations to carbon tetrachloride are assessed under the EPA NATA. The 2014 NATA reports a national ambient carbon tetrachloride concentration of 0.53 µg/m^3 and 3 in a million cancer risk. https://www.epa.gov/national-air-toxics-assessment/2014-nata-assessment-results#pollutant

SACC	**SACC COMMENTS:** Recommendation: Exclusions of conditions of use during problem formulation should be made more explicit in the risk evaluation rather than referencing the Scope of Work. For example, present them in a summary table with the reasons for exclusion.	Clarifying language about what pathways are under the jurisdiction of other EPA-administered statutes has been added to Section 1.4.3 of the Risk Evaluation.
43	**PUBLIC COMMENTS:** The final risk evaluation must address both acute and chronic consumer exposure to CCl4. While the consumer products listed above result in short-term exposure to CCl4, these products (particularly household) may be used repeatedly over time and consumers are exposed to CCl4 in indoor and outdoor air on a continuing basis. Thus, cancer and noncancer risks to consumers could be significant and should be assessed and included in a risk evaluation that encompasses all intended, known, and reasonably foreseeable conditions of use.	Chronic exposure scenarios resulting from long-term use of household consumer products are likely to be relatively infrequent with short durations of use. In addition, the short half-life of the chemicals in the body does not result in significant accumulation between uses on different days. Therefore, even if levels of carbon tetrachloride in consumer products were measurable, use frequencies would be considered to be too low to create chronic risk concerns.
26	**PUBLIC COMMENTS:** EPA claims "there [is] no data supporting its use in the [aerospace] industry" (p. 29). EPA's source for this assumption is a personal communication with the Aerospace Industries Association (AIA), which EPA has not corroborated, and the substance of which EPA has not made available. The email communication directly contradicts an earlier comment submitted by AIA, which states: "The aerospace industry uses products/formulations containing CCl4 in the manufacture, operations and maintenance of aerospace products. CCl4 has been identified in limited use in specific adhesives (including methacrylate), and for specific cleaning operations."	All reasonably available information, including AIA's response stating that the previously identified products in their comment have been discontinued and the lack of data supporting the use of carbon tetrachloride in the industry, indicate that there is no known, intended, or reasonably foreseen use of carbon tetrachloride in the aerospace industry. In addition, the Montreal Protocol and CAA Title VI prohibit the direct use of carbon tetrachloride in the formulation of commercially available products for industrial/commercial/consumer uses, including aerosol and non-aerosol adhesives and cleaning/degreasing solvent products, except as a laboratory chemical.
26	**PUBLIC COMMENTS:** EPA states that it "found no evidence to suggest that the manufacturing of ibuprofen, or any other pharmaceuticals,	While use of carbon tetrachloride as a process solvent in the manufacture of pharmaceuticals was included in the problem formulation, upon further analysis, EPA has determined that

	still utilizes CCl4 or that such use is reasonably foreseen to resume." However, a cursory Google search suggests that CCl4 is still used in the manufacturing of pharmaceuticals: • Parchem, American Elements, and Olin Chlorinated Organics advertise uses of CCl4 related to pharmaceutical manufacturing. • A 2019 Market Watch report listed pharmaceutical as the first in a list of "markets by application" for CCl4. EPA has failed to rely on all reasonably available information. EPA has broad authority under TSCA to mandate submissions from industry that would reveal whether or not this chemical's use as process agent in the manufacturing of pharmaceuticals is a condition of use. The SACC should recommend EPA exercise this authority to obtain information that could be used to confirm or negate its assumptions.	this use falls outside TSCA's definition of "chemical substance." Under TSCA § 3(2)(B)(vi), the definition of "chemical substance" does not include any food, food additive, drug, cosmetic, or device (as such terms are defined in section 201 of the Federal Food, Drug, and Cosmetic Act) when manufactured, processed, or distributed in commerce for use as a food, food additive, drug, cosmetic, or device. EPA has concluded that carbon tetrachloride use as a process solvent during pharmaceutical manufacturing falls within the aforementioned definitional exclusion and is not a "chemical substance" under TSCA. Further, as stated in the draft risk evaluation, EPA does not have any evidence that carbon tetrachloride is still being used in the manufacture of ibuprofen or any other pharmaceuticals. The fact that distributors of carbon tetrachloride cite pharmaceutical manufacturing as one of the uses of the chemical substance does not by itself indicate that it is being used for this purpose.
31	**PUBLIC COMMENTS:** EPA used qualitative assumptions to indicate that exposure potential was low for reactive ion etching and laboratory use. The SACC should consider the appropriateness of these assumptions and provide recommendations regarding the use of qualitative approaches to support assumptions of minimal exposure.	EPA requested information on all aspects of risk evaluations of carbon tetrachloride throughout the risk evaluation process, including opening public dockets for receipt of such information, conducting outreach to manufacturers, processors, users and other stakeholders. The information received have been incorporated into the risk evaluation. The TSCA risk evaluation strategies refer to study guidelines along with professional judgment as helpful guidance in determining the adequacy or appropriateness of certain study designs or analytical methods. EPA considered reasonably available, relevant data and information that conform to the TSCA science standards when developing the risk evaluation of carbon tetrachloride.

		Due to the performance requirements of products typically produced via Reactive-ion etching (RIE), carbon tetrachloride is generally applied in small amounts in a highly controlled work area (e.g., under a fume hood as per good laboratory practice), thus eliminating or reducing the potential for exposures.
40	**PUBLIC COMMENTS:** The final risk evaluation should clarify that conclusions of unreasonable risk do not extent to substances that are not "chemical substances" as defined in TSCA § 3(a) and that the findings are described only to form a basis for evaluating risk from conditions of use that are governed by TSCA. Pesticides, tobacco, certain nuclear material, firearms, shells and cartridges, food, food additives, drugs, cosmetics, and medical devices are excluded from the TSCA definition of "chemical substance."	Section 1.4.2 of the risk evaluation specifies that the term "chemical substance" as defined in TSCA § 3(2) does not include any mixture; any pesticide when manufactured, processed, or distributed in commerce for use as a pesticide; tobacco or tobacco product; source material, special nuclear material, or byproduct material; any article the sale of which is subject to the tax imposed by section 4181 of the Internal Revenue Code of 1986; and any component of such an article, or any food, food additive, drug, cosmetic, or device when manufactured, processed, or distributed in commerce for use as a food, food additive, drug, cosmetic, or device. For this reason, any conclusions of unreasonable risk do not extend to substances that are not defined as chemical substances under TSCA § 3(2).
SACC	**SACC COMMENTS:** Recommendation: The justification for regrouping conditions of use should be described in more detail wherever it was conducted. Surrogate groups should be named more specifically to distinguish different types. For example, a chemical surrogate is different from a worker activity surrogate, although the draft risk evaluation seems to conflate the two. The term "surrogate data" can mean different things, with different levels of uncertainty. • One example is applying monitoring data for the target chemical to a different condition of use, as in	The regrouping of conditions of use is described in section 2.4.1.6 of the risk evaluation. In addition, EPA expanded discussions in the final risk evaluation regarding the type of surrogate data utilized and the associated assumptions in Section 4.4.1 of the risk evaluation.

	the case of the manufacturing and processing condition of use. The assumptions in this case are multiple (similar source types, similar processes, similar worker activities, etc.). • Another example is using monitoring data for a chemical other than the target (which was not measured) on the basis that the surrogate chemical has similar physicochemical properties (or differences in exposure concentrations could be estimated from the properties). This type of surrogate requires fewer assumptions and is likely to introduce lower uncertainty in exposure estimates than in the first example. • EPA's hierarchy of exposure estimation approaches does not distinguish between these two, although they would be expected to have different levels of uncertainty, and both seem to co-mingle in the draft risk evaluation. It can be argued also that EPA uses workers' exposures as the surrogate for estimating exposures to ONUs, which is yet another application of the term "surrogate." Recommendations: (1) Be specific when using the term "surrogate" when applying data from one condition of use to another; (2) ensure that the condition of use and its surrogate do not have hugely different associated levels of uncertainty; and (3) better describe the engineering and worker activities associated with a condition of use and compare these to their surrogate condition of use to ensure that they are not significantly different.	
26	**PUBLIC COMMENTS:**	The frequency and magnitude of take-home exposure is dependent on several factors, including personal hygiene and

	EPA excluded a number of reasonably foreseen conditions of use in the workplace that should have been evaluated, including: exposures from spills in the workplace; "take-home exposures;" exposures of maintenance staff, especially those cleaning up spills and leaks; and exposures of workers at small or medium facilities where assumptions of routine PPE use or other protections are less likely to be valid. Each of these is a "reasonably foreseen" aspect of the circumstances under which CCl4 is manufactured, processed, distributed, used, or disposed of.	visibility of the chemical on skin or clothing. EPA does not have methods to reliably predict take-home exposure. Spills and leaks generally are not included within the scope of TSCA risk evaluations because in general they are not considered to be circumstances under which a chemical substance is intended, known or reasonably foreseen to be manufactured, processed, distributed, used, or disposed of. To the extent there may be potential exposure from spills and leaks, EPA is also declining to evaluate environmental exposure pathways addressed by other EPA-administered statutes and associated regulatory programs. See response for question about spills under Charge Question 1 for additional detail.
General population exposures		
SACC	**SACC COMMENTS:** Recommendation: Include a summary of residential indoor and outdoor air concentrations of CCl4 as well as personal air concentrations of the residents. • This information would provide more context for EPA's decision to not evaluate consumer exposures, as it did in the evaluation for methylene chloride. The sources for these data are the same as those cited in that evaluation.	In accordance with the CPSC ban, carbon tetrachloride is not identified in the California Air Resources Board consumer product database and no consumer uses are listed in the CDR. Consumer products and/or commercial products containing chlorinated compounds made with carbon tetrachloride as a process agent are available for public purchase at common retailers [EPA-HQ-OPPT-2016-0733-0003, sections 3 and 4, (U.S. EPA, 2017)]. However, these products are not expected to contain measurable amounts of carbon tetrachloride because carbon tetrachloride is not used in the manufacturing of the actual products. Trace levels of carbon tetrachloride in the chlorinated substances used to manufacture the products are expected to volatilize during the product manufacturing process. Concentrations of carbon tetrachloride along with other 37 gas-phase organic air toxics were measured by Logue et al.

		(2010) over a 2-year period at four different sites in and around Pittsburgh, PA: a downtown site with substantial mobile source emissions; two residential sites adjacent to one of the most heavily industrialized zones in Pittsburgh; and a regional background site. Concentrations of carbon tetrachloride exhibited little temporal or spatial variability with study average concentrations of carbon tetrachloride varied by less than 25% across the four sites. In a separate study, carbon tetrachloride was measured and interpreted by de Blas et al. (2016) with high-time resolution in two sites (urban and rural) in Northern Spain. One site is an urban area influenced by the surrounding industry, where measurements were performed for a one-year period (2007–2008) and the second site is a rural background area where measurements were carried out for a non-successive five-year period (2003–2005, 2010–2011, and 2014–2015 years). Median yearly carbon tetrachloride mixing ratios (a dimensionless parameter indicates the abundance of one component of a mixture relative to that of all other components) were higher in the urban area (120 parts per trillion by volume) than in Valderejo Natural Park (80–100 parts per trillion by volume). The carbon tetrachloride was reported by de Blas et al. (2016) to be well mixed in the atmosphere and no sources were reported to impact the rural site. In the urban areas chlorine-bleach products that are used as indoor cleaning agents could result a potential source of carbon tetrachloride due to reactions with organics, soap or surfactants. Furthermore, background concentrations to carbon tetrachloride are assessed under the EPA NATA.
SACC, 23, 26,	**SACC COMMENTS:** • The current exclusion of exposure pathways to the general population through releases to ambient air,	As part of the Problem Formulation for carbon tetrachloride (U.S. EPA, 2018b), EPA found that exposures to the general population may occur from the conditions of use due to

32, 38, 41, 43	drinking water, ambient water, biosolids, and disposal pathways could lead to underrepresentation of the risks. Recommendation: Consider performing a wider assessment accounting for these excluded pathways, which will provide a more reliable measure of the risk. **PUBLIC COMMENTS:** There is extensive evidence of pervasive general population exposure to CCl4 from releases to air, water, and soil and at levels in ambient air and drinking water that present significant cancer risks. Large air emissions of CCl4 raise health concerns for the general population and subpopulations living near emission sources. • Recent TRI and NEI reporting and scientific studies indicate substantial ongoing emissions of CCl4. The NTP Report on Carcinogens states that "8 million people living within 12.5 miles of manufacturing sites were possibly exposed to CCl4 at an average concentration of 0.5 μg/m^3 and a peak concentration of 1,580 μg/m^3." • ATSDR reports that: "Based on analysis of 4,913 ambient air samples reported in the National Ambient VOCs Database, the average concentration of CCl4 was 0.168 ppb (1.1 μg/m^3)." It estimates that daily intake from air ranges from 12 to 511 μg/m^3, based on average ambient concentrations of 0.1-4 ppb (0.64-25.6 μg/m^3). • A review of EPA's air toxics data reveals that every census tract in the U.S. has excess cancer risk of about 3.5 in a million due to CCl4 in the air. • EPA and USGS report that CCl4 has been consistently	releases to air, water or land. The exposures to the general population via surface water, drinking water, ambient air and sediment pathways fall under the jurisdiction of other environmental statutes administered by EPA, *i.e.*, CAA, SDWA, CWA, and RCRA. As explained in more detail in section 1.4.3 of the final risk evaluation, EPA believes it is both reasonable and prudent to tailor TSCA risk evaluations when other EPA offices have expertise and experience to address specific environmental media, rather than attempt to evaluate and regulate potential exposures and risks from those media under TSCA. EPA believes that coordinated action on exposure pathways and risks addressed by other EPA-administered statutes and regulatory programs is consistent with the statutory text and legislative history, particularly as they pertain to TSCA's function as a "gap-filling" statute, and also furthers EPA aims to efficiently use Agency resources, avoid duplicating efforts taken pursuant to other Agency programs, and meet the statutory deadlines for completing risk evaluations. EPA has therefore tailored the scope of the risk evaluations for carbon tetrachloride using authorities in TSCA sections 6(b) and 9(b)(1). See section 1.4.3 of the Risk Evaluation. Clarifying language about what pathways are under the jurisdiction of other EPA-administered statutes has been added to Section 1.4.3 of the Risk Evaluation.

	detected in drinking water supplies. ATSDR concludes that "[i]ngestion via contaminated drinking water is an important route of exposure for the general population not living in areas where CCl4 is extensively used" and that the general population may also inhale CCl4 "from volatilization of contaminated water during showering or bathing." There are more than 160 drinking water systems, serving more than one million people, with CCl4 levels exceeding health-protective standards. • The EPA problem formulation references a study from New Jersey Department of Environmental Protection that finds that the "acceptable shower water criteria for CCl4 is 0.15 μg/L and the associated shower air concentration of CCl4 would be acceptable at 1.5 x 10-5 μg/m3." The risk evaluation makes no effort to assess whether these "acceptable" concentrations are being exceeded. • Hundreds of federal Superfund sites with CCl4 in the soil or groundwater pose a potential threat of vapor intrusion. Vapor intrusion may provide a partial explanation for the widespread detection of CCl4 in indoor air. As ATSDR notes "Typical concentrations in homes in several U.S. cities were about 1 μg/m3 (0.16 ppb), with some values up to 9 μg/m3 (1.4 ppb)." These risks are not being effectively reduced under other environmental laws. • EPA's exclusion of environmental exposure pathways from risk evaluations will defeat the central TSCA goal of comprehensively evaluating a chemical's risks to humans and the environment, and the law's requirement for EPA to consider all conditions of use, including those affecting PESS.		

	• EPA has not explained why, in direct contradiction to how EPA treated background exposures from hexabromocyclododecane (HBCD) to the general population, it chose to entirely ignore background exposures to CCl4. • Under the National Air Toxics Assessment (NATA), EPA calculates the long-term health risks of CCl4 by considering background exposures to the chemical because it "has a very long residence time, which makes predictions based on current emissions moot." The SACC should comment on the human health impacts of EPA's failure to consider background exposures to CCl4.	
SACC, 23, 30, 32, 38, 41, 42, 43	**SACC COMMENTS:** Recommendation: Workplace exposure estimates should be aggregated. • Multiple SACC members favor aggregating contemporaneous exposures. **PUBLIC COMMENTS:** The Agency has not assessed aggregate exposures for CCl4 or made their unreasonable risk findings based upon combined exposures, either for a specific condition of use or with consideration of exposures from non-TSCA-related scenarios. TSCA provides protections to workers not just from chemical exposure in the workplace but from air emissions and other environmental releases as well as exposures to consumer products. CCl4 levels are likely to be ever greater surrounding the facilities where CCl4 is manufactured and released, which are the same communities where many of the workers employed in those facilities live. In tribal communities, a	TSCA section 6(b)(4)(F)(ii) directs EPA to "describe whether aggregate or sentinel exposures to a chemical substance under the conditions of use were considered, and the basis for that consideration" in risk evaluations. EPA defines aggregate exposures as the combined exposures to an individual from a single chemical substance across multiple routes (*i.e.*, dermal, inhalation, or oral) and across multiple pathways (*i.e.*, exposure from different sources). 40 CFR 702.33. EPA defines sentinel exposures as the exposure from a single chemical substance that represents the plausible upper bound of exposure relative to all other exposures within a broad category of similar or related exposures. 40 CFR 702.33. EPA considered the reasonably available information and used the best available science to determine whether to consider aggregate or sentinel exposures for a particular chemical. EPA has determined that using the high-end risk estimate for inhalation and dermal risks separately as the basis for the unreasonable risk determination is a best available science approach. There is low confidence in the result of aggregating

	substantial number of residents have multiple jobs and live near their community facilities, including disposal facilities. A single person may be a landfill worker, an occupational bystander, and a near-facility general population, as well as a consumer. The SACC has repeatedly raised concerns about EPA's failure to consider environmental pathways of human exposure. Environmental pathways play a major role in contributing to aggregate exposures and EPA's exclusion of them means that the Agency is not able to accurately assess risks, including to PESS. Congress directed EPA to make an unreasonable risk determination for the chemical substance as a whole, taking into account all of its uses. EPA violates that requirement in this risk evaluation, by proposing use-by-use determinations of unreasonable risk that fail to consider the risks to workers who are exposed from multiple conditions of use, despite noting that "it is not uncommon for employees at a facility to perform multiple types of tasks throughout the work day." EPA should prepare an exposure assessment that examines aggregate exposure, combining exposures from the inhalation and dermal pathways, including baseline exposures, under all conditions of use.	the dermal and inhalation risks for this chemical if EPA uses an additive approach, due to the uncertainty in the data. EPA does not have data that could be reliably modeled for the aggregate exposure, which would be a more accurate approach than adding, such as through a PBPK model. Using an additive approach to aggregate risk in this case could result in an overestimation of risk. Given all the limitations that exist with the data, EPA's approach is the best available science. EPA has added language to the Key Assumptions and Uncertainties section describing these assumptions and uncertainties. Clarifying language on exposure pathways and risks under the jurisdiction of other EPA-administered statutes have been added to section 1.4.3 of the final risk evaluation document. EPA did not consider carbon tetrachloride background exposure that workers might be exposed to in addition to exposures from TSCA conditions of use. This may result in an underestimation of risk, and additional discussion of this underestimation has been added to the document in the Key Assumptions and Uncertainties section.
Worker exposure estimation: methods, models, and data		
SACC	**SACC COMMENTS:** Recommendation: EPA should develop a decision tree for using monitoring data or modeling not just on the basis of the quality of monitoring data, but also on the quantity of data.	EPA considered both quality and quantity of monitoring data when deciding to pursue modeling. For many conditions of use, there were limited or no reasonably available data to develop and/or validate simulation models.

SACC, 38, 43	**SACC COMMENTS** SACC identified the following data gaps and uncertainties: lack of exposure data for the scenarios of ONU inhalation, reactive ion etching, processing agent/aid, additive use, laboratory use, waste handling, and dermal exposure; and limited data sets for specialty use. To increase confidence in risk conclusions, EPA will need to use its statutory authority to request limited studies to obtain the quality data to better support these parts of the assessment. This is particularly important for the determination of unreasonable risk for ONUs. One member noted that the availability of workplace measurements is low and that dependence upon modeling is, therefore, high in this draft risk evaluation. The Agency's hesitance to use its authority to request industry data was again noted by the Committee. **PUBLIC COMMENTS:** If employers did not voluntarily provide monitoring data, EPA has the authority to compel its production under TSCA section 8 or to issue subpoenas for "the production of … documents … that the administrator deems necessary" under section 11. In the event that no monitoring data exist for a condition of use, EPA can order the generation of such data under TSCA section 4. TSCA requires EPA to conduct risk evaluations based on "reasonably available" information, including information that EPA "can reasonably generate, obtain, and synthesize for use in risk evaluations." EPA must acquire and consider that available data, using its TSCA information-gathering authority to the extent needed	EPA did not find additional reasonably available information for these sources. EPA requested information on all aspects of risk evaluations throughout the risk evaluation process, including opening public dockets for receipt of such information, conducting outreach to manufacturers, processors, users and other stakeholders. The data received have undergone review and interpretations in the risk evaluation document. In addition, data available from the peer-reviewed literature are also included in the risk evaluation document. EPA had sufficient information to complete the carbon tetrachloride risk evaluation using a weight of scientific evidence approach. EPA selected the first 10 chemicals for risk evaluation based in part on its assessment that these chemicals could be assessed without the need for regulatory information collection or development. When preparing this risk evaluation, EPA obtained and considered reasonably available information, defined as information that EPA possesses, or can reasonably obtain and synthesize for use in risk evaluations, considering the deadlines for completing the evaluation. In some cases, when information available to EPA was limited, the Agency relied on models; the use of modeled data is in line with EPA's final Risk Evaluation Rule and EPA's risk assessment guidelines.

	EPA should conduct dermal exposure monitoring in representative workplaces.	
SACC, 26, 38, 45	**SACC COMMENTS:** One Committee member suggested that EPA partner with the OSHA or the NIOSH to get more sensitive sampling and analytical methods in use in order to allow estimation of exposure concentrations closer to 40 ppb or lower, to allow for actual detected levels. Another Committee member suggested that the amended TSCA law is a mechanism for starting a new discussion on occupational exposure measurement and that the PEL framework is no longer appropriate. **PUBLIC COMMENTS:** EPA does not discuss its consultation or coordination with the OSHA on risks to ONUs. TSCA Section 9(a) contemplates consultation between EPA and OSHA and authorizes OSHA to decide whether it agrees with EPA's risk determination concerning worker health. EPA must be more transparent in its risk evaluations about its consultations with OSHA. The CCl4 PEL is 50 years old and universally acknowledged to be unprotective. OSHA promulgated the PEL for CCl4 in 1971 based on research performed during the 1950s and 1960s, and largely based on acute health effects. In 1989, OSHA finalized an updated PEL for CCl4: a 2-ppm 8-hour TWA limit. For the original OSHA limit of 10 ppm, the cancer risk estimate for CCl4 was 17.9 excess deaths per 1,000 exposed workers. Even at the limit of 2 ppm, the predicted risk is 3.7 excess deaths per 1,000 workers. The rule was subsequently vacated by the Eleventh Circuit. As a result of this decision, the OSHA	EPA engages with all its federal partners as it works to conduct and refine its risk evaluations. In the 2017 Procedures for Chemical Risk Evaluation Under the Amended TSCA (82 FR 33726, July 20, 2017), EPA committed to, by codifying, interagency collaboration to give the public confidence that EPA will work with other agencies to gain appropriate information on chemical substances. This is an ongoing deliberative process and EPA is not obligated to provide descriptions of predecisional and deliberative discussions or consultations with other federal agencies. In the interest of continuing to have open and candid discussions with our interagency partners, EPA is not intending to include the content of those discussions in the risk evaluation. Comparison to the PEL is illustrative only for the purposes of discussing engineering and administrative controls. OSHA's Respiratory Protection Standard (29 CFR § 1910.134) requires employers in certain industries to address workplace hazards by implementing engineering control measures and, if these are not feasible, provide respirators that are applicable and suitable for the purpose intended. Engineering and administrative controls must be implemented whenever employees are exposed above the PEL. If engineering and administrative controls do not reduce exposures to below the PEL, respirators must be worn. Respirator selection provisions are provided in § 1910.134(d) and require that appropriate respirators are selected based on the respiratory hazard(s) to which the worker will be exposed and workplace and user factors that affect respirator performance and reliability.

	PEL for CCl4 remains at 10 ppm, the level adopted in 1971.	
SACC, 26, 38	**SACC COMMENTS:** Recommendation: Use measured OSHA data in the risk evaluation to inform "high end" exposures. • Monitoring data from OSHA and/or NIOSH inspections could be useful for informing exposure levels. One Committee member commented that the OSHA inspection data available online reports measured workplace levels up to 39.5 ppm, which is much higher than the "high end" exposure level reported in the draft risk evaluation. **PUBLIC COMMENTS:** For most other conditions of use, EPA did not seek or receive any monitoring data; however, this does not mean that such data do not exist. • OSHA requires employers to preserve and maintain employee exposure records for thirty years. A quick search of OSHA Chemical Exposure Health Data tool yielded 321 air samples for CCl4 collected as recently as March 2017. • OSHA's respirator standard also requires that employers "evaluate the respiratory hazards at their workplaces," including a quantitative determination of potential exposures. If respirators were as widely used as EPA assumes, employers would have significant amounts of workplace exposure data that would be reasonably available to EPA. If no such data exist, then EPA's assumptions of widespread and health-protective respirator use are wrong. EPA must acquire all of the relevant OSHA data in order to comply with the TSCA Section 26 requirement.	EPA is aware of the OSHA data and has reviewed over 300 data points for carbon tetrachloride in the OSHA CEHD. The reasons for not using these data are the lack of clarity and data quality on the conditions of use, the date of sampling, and/or inconsistencies in the sample durations and results. Examples included: • The samples reported as non-detects (ND) could be due to the absence of carbon tetrachloride at the site making the dataset not relevant to carbon tetrachloride; • All samples are short-term samples and not representative of full-shift exposures; • Samples were collected prior to the Montreal Protocol and CAA Title VI ban and could include exposures from phased-out uses; • The condition of use could be a non-TSCA use; and • Sample results did not include sample times such that the representativeness of operation and exposures are unknown. The reported respiratory protection and other PPE usages in workplace are included in the risk evaluation document with relevant citations. EPA reviewed all relevant and reasonably available OSHA data. OSHA data are collected as part of compliance inspections at various types of facilities. Certain industries are typically targeted based on national and regional emphasis programs. Other inspections may be prompted based on complaints or referrals. As a result, OSHA data may underrepresent PPE usage throughout the affected industry. Additionally, because EPA uses the high-end exposure values to account for

		uncertainties and variabilities in PPE usage, this is accounted for in its unreasonable risk determinations. EPA's approach for developing exposure assessments for workers is to use reasonably available information and expert judgment. When appropriate, in the risk evaluation, EPA will use exposure scenarios both with and without engineering controls and/or PPE that may be applicable to particular worker tasks on a case-specific basis for a given chemical. While EPA has evaluated worker risk with and without PPE, as a matter of policy, EPA does not believe it should assume that workers are unprotected by PPE where such PPE might be necessary to meet federal regulations, unless it has evidence that workers are unprotected. For the purposes of determining whether or not a condition of use presents unreasonable risks, EPA incorporates assumptions regarding PPE use based on reasonably available information and professional judgment underlying the exposure scenarios. These assumptions are described in the unreasonable risk determination for each condition of use, in section 5.2. Additionally, in consideration of the uncertainties and variabilities in PPE usage (*e.g.*, the burden associated with the use of supplied-air respirators, including the expense of the equipment and the necessity of fit-testing and training for proper use), EPA uses the high-end exposure value when making its unreasonable risk determination in order to address those uncertainties. EPA has also outlined its PPE assumptions in section 5.1. Further, in the final risk evaluation for carbon tetrachloride, EPA has determined that most conditions of use pose an unreasonable risk to workers even with the assumed PPE.

SACC	**SACC COMMENTS:** A Committee member found a potentially useful biomonitoring study conducted in Italy (Ghittori et al., 1994) that is not cited in the draft risk evaluation. That study collected both environmental and biomarker data for 55 workers exposed to CCl4 and potentially could provide a check on exposure estimates in the risk evaluation.	EPA reviewed the submitted study and incorporated the exposure monitoring data for the use of carbon tetrachloride in the revised risk evaluation document. Appropriate citation and interpretations also included in the risk evaluation document.
26, 38	**PUBLIC COMMENTS:** EPA determined that CCl4 presents no unreasonable risk to workers despite having no exposure data for many conditions of use and inadequate data for the others. EPA violated its statutory obligation to consider "reasonably available information" when evaluating chemical risks. • For CCl4 manufacturing, EPA relied exclusively on exposure data voluntarily submitted by the HSIA. HSIA's data cover only two manufacturing facilities, a small fraction of the facilities that manufacture or process CCl4. HSIA did not provide information about the conditions under which these samples were taken or the sampling protocols and methodology. • EPA also used this HSIA manufacturing data as a surrogate to estimate occupational exposures from the processing of CCl4 as a reactant, despite acknowledging that manufacturing data "are not directly applicable to processing of CCl4 as a reactant." • EPA relied on the HSIA data without questioning its reliability or representativeness. EPA provides no justification for its exclusive reliance upon this potentially biased data without independent validation and quality assurance reporting.	The data gathering effort to support the risk evaluation was performed by literature searches and leveraging existing industry-specific information. HSIA data were provided as part of continuous industrial hygiene monitoring programs and were evaluated using the same criteria as other data sets. The reasonably available data readily attributable to manufacturing and processing of carbon tetrachloride were limited and contained their own deficiencies (such as the age of the studies, lack of discrete data points, and no metadata information) resulting in low quality ratings. Additionally, limited exposure data exists due to manufacturing, processing, and use restrictions enforced under the Montreal Protocol, CAA Title VI, and the Consumer Product Safety Commission ban.
29	**PUBLIC COMMENTS:** Each facility that manufactures CCl4 performs a documented Qualitative Exposure Assessment in which	EPA does not assess worker exposure through Similar Exposure Groups (SEGs) because EPA does not have information available to determine these groups based on the

	tasks are assessed and characterized. Components of the Qualitative Exposure Assessment include full-shift exposure description, a description of each task that may contribute to the overall full-shift exposure, and the frequency/duration/PPE/controls for each task. • Each facility divides employees into Similar Exposure Groups (SEGs), groups of workers having the same general exposure profile because of the similarity and frequency of the tasks performed, materials used, processes, and controls. • Monitoring data collected for each exposure group is analyzed to determine the overall exposure potential. If the 95th percentile analysis results are below the applicable Occupational Exposure Limits (OELs), then the exposures are considered acceptable and periodic monitoring/reassessments are performed to confirm/ validate. Any individual sample results exceeding applicable OELs is investigated to determine cause(s) and mitigated.	provided worker activity descriptions. Facility personnel conducting the monitoring intimately know the facility and can interview workers to determine SEGs. Additionally, worker activities and job titles are determined differently at each facility making an equal comparison very difficult; therefore, EPA has relied only on designations between workers and ONUs.
45	**PUBLIC COMMENTS:** EPA should delineate a tiered human or environmental exposure modeling approach for TSCA draft risk evaluations. This approach will allow EPA to identify and focus on uses that are high exposure and devote more resources to determining potential risk presented by those uses. We propose the Tank Truck and Railcar Loading and Unloading Release and Inhalation Exposure Model as a screening level exposure assessment for all occupational conditions of use that use closed systems. Any conditions of use that indicate high risk would move to further analyses and data to confirm high risk levels.	The use of the Tank Truck and Railcar Loading and Unloading Release and Inhalation Exposure Model as a screening level tool to determine if further analyses are required, as suggested in the comment, is inappropriate. This model only accounts for exposures during the loading/unloading of bulk containers which is likely only a portion of the workday and may underestimate total exposures as described in the uncertainties section of the risk evaluation document. This estimate could be appropriate for certain conditions of use where the chemical is primarily used in closed systems such that the unloading activity is expected to be the primary exposure activity. However, there could be other conditions of use where the chemical is used in open systems that results in significantly higher levels of exposure

		than estimated by the Tank Truck and Railcar Loading and Unloading Release and Inhalation Exposure Model.
31	**PUBLIC COMMENTS:** The SACC should consider whether it is appropriate for EPA to estimate inhalation exposure with a modeling approach using the Tank Truck and Railcar Loading and Unloading Release and Inhalation Exposure Model when monitoring data from tank truck and railcar loading and unloading are available.	EPA updated the risk evaluation of carbon tetrachloride to assess the worker exposure during import and/or repackaging of carbon tetrachloride from the tank truck and railcar loading and unloading data identified from the monitoring data submitted by HSIA. Fifteen of the 356 submitted data listed worker activities for the unloading and/or loading of carbon tetrachloride into tank trucks or railcars. For this assessment, EPA only considered the 8-hr TWA data as information to substantiate 12-hr shifts at repackaging sites were not identified. Additionally, EPA only used data points if the worker activities were specifically for carbon tetrachloride loading/unloading.
ONU exposure estimation: methods, models, and data		
SACC	**SACC COMMENTS:** Recommendations: Attempt estimation of ONU exposures where data permit as a check on default assumption of mean worker exposure. Consider a hierarchy of ONU exposures to distinguish extremes within that classification. • EPA's description of the approach and assumptions for deriving ONU's exposure estimates are adequately transparent; however, scientific validity is questionable because the uncertainties, while well described, are considerable (due in part to data scarcity). • The Agency could use the job categories classified as ONUs and additional considerations to derive ONU exposure estimates. In addition, it should be possible to use exposure or area modeling for at least some of the conditions of use (for which EPA has, or can request, data), as a comparison check for exposure estimates.	EPA used a subset of worker data to assess ONU exposure where appropriate. EPA has included appropriate modeling considering the available data. In the 'Uncertainties' Section 4.3.2.1, the revised document included: "ONUs are likely a heterogeneous population of workers, and some could be exposed more than just occasionally to high concentrations."

	• One member suggested that the number of sites actively using CCl4 was not so large that EPA could not request or attempt data collection in a meaningful sample.	
SACC, 22, 29, 39	**SACC COMMENTS:** • One SACC member requested clarification as to whether HSIA data that appear to be pertinent to ONU exposures had been received by EPA and used in the draft risk evaluation. Those data involve 7 full shift samples collected from administrative/supervisory personnel, so it is likely that these are ONU samples. Concentrations were <0.063-0.066 ppm (under the LOD of the method). • One Committee member noted that public commenters indicated that there are monitoring data relevant for ONUs in the manufacturing and processing sectors that may be useful to the Agency to consider. Recommendation: Explain why it was decided not to use the HSIA administrative/supervisory personnel data, even if only to compare them to the exposure estimates for ONUs. There is concern that this may be construed as data selection bias. **PUBLIC COMMENTS:** Monitoring data on workers at CCl4 production facilities were submitted to EPA as part of HSIA's comments on the CCl4 problem formulation document. The data included personal breathing zone measurements from both workers and ONUs. • EPA did not note that certain exposure groups (*i.e.*, process supervisors, electricians, utilities control board technicians) were ONUs and wrongly concluded that exposure data for ONUs were unavailable.	EPA received the additional information from HSIA to denote ONU exposure data (EPA-HQ-OPPT-2019-0499-0022) and has incorporated the ONU data into the risk evaluation for carbon tetrachloride. These data were used in the draft risk evaluation but were previously grouped with worker exposure data. As recommended by the SACC comment, EPA has revised the assessment to separate these data from the worker exposure estimate and used these data to assess ONUs. A total of 17 datapoints were included as ONU exposure data according to the additional comment provided by HSIA, EPA-HQ-OPPT-2019-0499-0022. These data include the 7 full shift samples mentioned in the range <0.063-0.066 ppm. The HSIA data denoting exposure for administrative/supervisory personnel data were included in the ONU exposure assessment for manufacturing. The ONU exposure data identified by the commenter are not all non-detect values. However, approximately 60% of the identified data is below the level of detection. To estimate exposures from these data, EPA used the *Guidelines for Statistical Analysis of Occupational Exposure Data*, which is summarized in Section 1.4.4.2 of the Supplemental Information on Releases and Occupational Exposure Assessment. For scenarios where ONU data is unavailable, EPA assessed ONU exposures at the worker central tendency. The uncertainties of this approach are described in Section 4.4.1

	• In response to this oversight, HSIA submitted to EPA ONU monitoring data of 17 breathing-zone full shift samples showing that exposures are below the detection limit (<0.063 to <0.21 ppm). The detection limit provided is likely still much higher than actual exposures since the evidence is based entirely on non-detects. • These data demonstrate that using the Workers' Central Tendency exposure concentration as a surrogate for ONUs is overly conservative. EPA should use the ONU monitoring data that were provided in the docket and consider using the central tendency estimate of the ONU data. This approach would still be considered a conservative estimate since it is based entirely on non-detect concentrations.	of the risk evaluation and such estimates are categorized as "low confidence."
38	**PUBLIC COMMENTS:** The broad range of workers are EPA defines as ONUs is too large to support any single classification. Under EPA's definition, ONUs may include cleaning workers, skilled trade workers, supervisors, and managers. But supervisors have very different exposure patterns than skilled trade workers and cleaning workers, and thus face very different risks from CCl4. EPA uses the central tendency (50th percentile) of worker inhalation exposures to calculate ONU risks, as opposed to collecting ONU-specific data or using the higher end exposure estimates that EPA uses for other workers. Particularly over a short period (*e.g.*, response to a spill or equipment maintenance), ONU exposures may be as great as or greater than other workers, and ONUs are even less likely to be provided PPE. EPA's failure to collect ONU-	EPA included ONUs who are defined in section 2.4.1 as "*working in the general vicinity of workers but do not handle chemical substances and do not have direct dermal contact with chemicals being handled by the workers*." Maintenance staff, cleaning workers, and skilled trade workers are a subset of ONUs and as such are not excluded from the risk evaluation. EPA considers ONUs to be a subset of workers for whom the potential inhalation exposures may differ based on proximity to the exposure source. For the majority of carbon tetrachloride conditions of use, the difference between ONU exposures and workers directly handling the chemical cannot be quantified. EPA assumed an absence of PPE for ONUs, since ONUs do not directly handle the chemical and are instead doing other tasks in the vicinity of carbon tetrachloride use. EPA assumed that, in most cases, ONU

	specific data and its reliance on central tendency exposure estimates understates the risks to ONUs. EPA assumes that ONUs will have no dermal exposures, an assumption that is unfounded for cleaning workers and skilled trade workers.	inhalation exposures are assumed to be lower than inhalation exposures for workers directly handling the chemical substance. For dermal exposures, EPA assumed that ONUs do not have direct contact with carbon tetrachloride; therefore, non-cancer effects and cancer from dermal exposures from carbon tetrachloride generally were not assessed.
22, 31, 39	**PUBLIC COMMENTS:** The SACC should review EPA's assumption that ONUs are exposed at the central tendency exposure concentration (50th percentile) of workers for manufacturing and processing uses. This assumption is overly conservative and not supported by the ONU personal exposure monitoring data submitted to EPA for manufacturing and processing uses. • Using the central tendency value implies that ONU exposures are 4-fold lower than those of workers in the near-field. This implication does not align with the data provided to EPA. • To the extent there are residual data needs for ONUs, a more appropriate approach to estimate ONU exposures is the use of ONU-specific exposure models. A cursory evaluation of near and mid-field plume model shows a large drop off in concentration with distance. Use of the same generation rate and air speed calculated for the Tank Truck and Railcar Loading and Unloading Release and Inhalation Exposure Model in the near-field plume model results in a nearly 50-fold reduction in concentration at a distance of 0.1-1 meter from the source. • Improvement of the assumptions regarding the mid- and far-field exposures would have a major impact on the risk characterization for cancer inhalation.	Where EPA had monitoring or modeled data specific to ONUs, unreasonable risk determinations were made based on high-end exposures. For conditions of use where the data did not distinguish between worker and ONU inhalation exposures, there was uncertainty regarding ONU exposure. ONU personal exposures are assumed to be lower than personal exposures for workers directly handling the chemical substance. To account for this uncertainty, EPA considered the workers' central tendency risk estimates from inhalation exposures when determining ONUs' unreasonable risk (rather than the high-end inhalation exposures), when data specific to ONUs was not available. ONU distance from users are accounted in the uses with Near-Field/ Far-Field modeling, which is superior to a method that would use the inverse square law. EPA does not have a method to account for air exchange rates for potential use of the inverse square law nor reasonably available data or information to estimate distance of ONUs from users in the other assessed uses.

	The SACC should consider whether the findings of unreasonable risks for ONUs are appropriate given that they are based on the application of worker inhalation monitoring data to ONUs.	
26	**PUBLIC COMMENTS:** EPA underestimated exposure to ONUs by assuming ONUs experience the central tendency exposures calculated for workers in the absence of PPE because EPA does not have any monitoring data or modeling specific to ONUs.	EPA considers ONUs to be a subset of workers for whom the potential inhalation exposures may differ based on proximity to the exposure source. For the majority of carbon tetrachloride conditions of use, the difference between ONU exposures and workers directly handling the chemical cannot be quantified. EPA assumed an absence of PPE for ONUs, since ONUs do not directly handle the chemical and are instead doing other tasks in the vicinity of carbon tetrachloride use. EPA also assumed that, in most cases, ONU inhalation exposures are assumed to be lower than inhalation exposures for workers directly handling the chemical substance. For dermal exposures, EPA assumed that ONUs do not have direct contact with carbon tetrachloride; therefore, non-cancer effects and cancer from dermal exposures from carbon tetrachloride generally were not assessed. To account for those instances where, based on EPA's analysis, the monitoring data or modeling data for worker and ONU inhalation exposure could not be distinguished, EPA considered the central tendency risk estimate when determining ONU risk.
22, 29, 39	**PUBLIC COMMENTS:** ONUs are protected from exposure by engineering and administrative controls. • If an ONU is in the immediate work environment when a worker is required to use specific PPE for a task, the ONU is required to use the same PPE as the worker. • Employees, contractors, and visitors are not allowed in manufacturing areas without appropriate PPE and safety training. Locker rooms and lunchrooms are	EPA considers ONUs to be a subset of workers for whom the potential inhalation exposures may differ based on proximity to the exposure source. For the majority of carbon tetrachloride conditions of use, the difference between ONU exposures and workers directly handling the chemical cannot be quantified. EPA assumed an absence of PPE for ONUs, since ONUs do not directly handle the chemical and are instead doing other tasks in the vicinity of carbon tetrachloride use. EPA also assumed that, in most cases, ONU

	located outside the manufacturing areas. No food or drinks are allowed in manufacturing areas. • The CCl4 production process is a closed system located in an outdoor area. The only production tasks that are not closed system involve pulling samples and collecting waste from the process. These are short, intermittent tasks (15-30 minutes) performed in the production area by trained employees, wearing appropriate PPE. • For maintenance employees performing tasks outside the production area, a perimeter is established with a barricade providing a buffer around the area. Real-time monitoring is done to ensure the buffer prevents exposure for employees working around the production area. Anyone working inside the barricaded area must wear appropriate PPE. • The assumption of significant exposures in the absence of respiratory protection is not consistent with current industrial practice. • Even if an ONU is in the general work area, it is unlikely that an ONU would be there for a full shift.	inhalation exposures are assumed to be lower than inhalation exposures for workers directly handling the chemical substance. For dermal exposures, EPA assumed that ONUs do not have direct contact with carbon tetrachloride; therefore, non-cancer effects and cancer from dermal exposures from carbon tetrachloride generally were not assessed. To account for those instances where, based on EPA's analysis, the monitoring data or modeling data for worker and ONU inhalation exposure could not be distinguished, EPA considered the central tendency risk estimate when determining ONU risk.
26	**PUBLIC COMMENTS:** EPA underestimated exposure to ONU by assuming ONUs are only present in the "far field zone." ONUs may not stay within the "far field zone" when they are responding to spills, maintaining equipment, and otherwise performing work activities that take them within the "near-field" workers zone. ONUs may regularly pass into each other's space to communicate or otherwise interact.	The evaluation of carbon tetrachloride exposure to ONUs does not use any near-field/far-field models in the evaluation.
Dermal exposure assumptions		
SACC	**SACC COMMENTS:** The SACC report includes a list of dermal parameters that are recommended for inclusion in the table of physical-	The Section 2.4.1.8 (Dermal Exposure Assessment) has been updated with inclusion of a conceptual diagram (Figure 2-4), and several dermal exposure scenarios of carbon tetrachloride

	chemical properties or elsewhere in the risk evaluation. These include aqueous permeability coefficients, relative permeability of the stratum corneum to that of the viable epidermis, theoretical maximum steady-state flux, octanol/air partition coefficient, stratum corneum/gas partition coefficient, dermal vapor to inhalation dose ratio (measured and modeled), and observed absorption flux. Descriptions, rationales, and references for each parameter are provided in the SACC report. • A Committee member reported that EPA was again using a percent absorbed approach based on the Frasch (2012) interpretation of the work by Kasting and Miller (2006). The Agency had previously switched to the Frasch and Bunge (2015) paper, which deals with absorption of the "skin depot" (post exposure) rather than the initial load. The Committee did not verify that the numerical results are correctly computed, but the change in approach is appropriate. • One member noted that for VOCs, in the absence of PPE, inhalation would be expected to dominate dermal vapor exposure. However, if respiratory protection, but not whole-body vapor protection is provided, dermal vapor exposure can exceed (PPE-reduced) inhalation exposure. For instance, if the ratio of inhalation dose to dermal vapor dose is 10 and an APF of 25 is assumed, the dermal vapor dose becomes the dominant exposure pathway.	from the IHSkinPerm© (developed by American Industrial Hygiene Association) output using the physical-chemical properties are summarized in Table 2-23. Description of the conceptual diagram, synopsis of existing tools/models, interpretations, and citations of references are also included in the risk evaluation document.
SACC	**SACC COMMENTS:** Experience in the occupational agriculture sector does suggest that hands are disproportionately exposed. The hand area data were obtained from the Exposures Factors	The Section 2.4.1.4 of risk evaluation document already clarified the basis for contact surface area of 1,070 cm^2 as an input parameter for estimating high-end dermal exposure to

	Handbook, which in turn derived the estimates from the Center for Disease Control and Prevention (CDC) National Health and Nutrition Examination Survey (NHANES) data. The Agency could use distributed values for hand surface area as those are available. Section 2.4.1.8 presents a good discussion. However, EPA does not have comparable data for many other assumptions.	liquids. This clarification also included that the above value is equivalent to the 50th percentile surface area of two-hands for males, the highest exposed population. EPA has no reasonably available information on actual surface area of contact with liquid and that the value is assumed to represent an adequate proxy for a high-end surface area of contact with liquid that may sometimes include exposures to much of the hands and also beyond the hands, such as wrists, forearms, neck, or other parts of the body, for some scenarios. The above statement also has been included in the Section 2.4.1.4 of risk evaluation document.
43	**PUBLIC COMMENTS:** EPA should model a broader range of dermal contact scenarios based on its own analysis of variations in dermal exposure conditions.	Based on the variety of number of potential worker exposure scenarios, EPA considered a general dermal exposure scenario and used parameters that provide a conservative estimate.
32, 43	**PUBLIC COMMENTS:** The basis for the dermal assessment was highly uncertain because of the limited data available. • Without test data on dermal absorption rates, EPA assumed that "the calculated retained dose is low for all dermal exposure scenarios as CCl4 evaporates quickly after exposure." EPA estimated that "approximately four percent of the applied dose is absorbed through the skin" where no gloves are worn and considerably less in instances of glove use. • EPA assumed no dermal exposure by ONUs. • As EPA acknowledged, rapid volatilization after skin contact would not occur in all situations; repeated skin contact with chemicals could have even higher than expected exposure if evaporation of the chemical occurs and the concentration of chemical in contact with the skin increases; wearing of gloves could have important consequences for dermal uptake; and without	These assumptions were primarily based on the *EPA 2-Hand Dermal Contact with Liquid Model*, which is generally consistent across all risk evaluations. EPA did not find reasonably available empirical data to develop alternate estimates of dermal exposure.

	any gloves, a splash of the liquid or immersion of the hand may overwhelm the skin contamination layer …if it is undiluted, then uptake could proceed rapidly. EPA did not develop alternate estimates of dermal exposure showing higher levels of absorption in these scenarios.	
26, 32, 38, 43	**PUBLIC COMMENTS:** EPA provides little justification for the assumption of a single dermal exposure event per day. It seems likely that workers would regularly engage in activities that could result in multiple exposure events per day. EPA acknowledges that this assumption "likely underestimates exposure" but did not to consider those risks or provide any sort of uncertainty analysis. This is an admitted violation of TSCA EPA should base dermal exposure scenarios in the final CCl4 evaluation on an assumption of multiple exposure events per day.	EPA has described events per day (FT) as one of the uncertainties for dermal modeling in the discussion of occupational dermal uncertainties (Section 4.4.1). This discussion also included that the assumption on the number of events likely underestimates exposure as workers could have repeated contacts with carbon tetrachloride throughout their workday.
38	**PUBLIC COMMENTS:** EPA improperly assumes worker exposures to CCl4 terminate "at the end of the task, shift, or work day." EPA offers no evidence that all workers clean hands and other exposed body parts following each shift. In the absence of cleaning, dermal exposure durations – and associated risks – may be greater than those estimated by EPA. Clothing can absorb CCl4, and many workers return home in the same clothes they wear at work. This absorption creates that potential for additional "take home" exposures that EPA has not addressed in its draft risk evaluation.	The frequency and magnitude of take-home exposure is dependent on several factors, including personal hygiene, good laboratory/industrial practices, and extent and visibility of the chemical on skin or clothing. EPA does not have methods to reliably predict take-home exposure.
39	**PUBLIC COMMENTS:** Considering the conservatism in the dermal exposure assumptions, the likely actual estimates for dermal cancer risk would be below the $1x10^{-4}$ benchmark. For most tasks that involve dermal exposure in chemical manufacturing	EPA has included an explanation of the dermal exposure assessment parameter assumptions in the Section 2.4.1.4. EPA stated that the value for the contact surface area is equivalent to the 50th percentile surface area of two-hands for males, the highest exposed population. EPA has no

	(*e.g.*, sampling a process line or hooking up a transfer line), there is no likely routine skin contact and certainly not hours each day. In most routine tasks with any liquid present, chemical-protective gloves would be used. Any liquid spills will land on the outside of a glove and largely evaporate. The full hand surface (or two full hands) would never be covered with liquid under any normal routine scenario.	reasonably available dermal exposure data, including information on actual surface area of contact with liquid.
Exposure uncertainty discussion/confidence ratings		
SACC	**SACC COMMENTS:** Recommendation: Levels of confidence should be provided for each route of occupational exposure, in addition to the overall result. • One member suggested that levels of confidence should be provided for each route of exposure, in addition to the overall confidence. In addition, that member thought that the text should include a more extensive summary discussion of confidence. • The Committee was of mixed opinion on the merits of the graphical depiction of the confidence ratings in Table 2-19. One Committee member commented that the scale and use of color implies a quantification that the Agency does not have. • One member noted that Section 4.4.1 does not describe uncertainties of exposure estimates derived with the Tank Truck and Railcar Loading and Unloading Release and Inhalation Exposure Model.	EPA included confidence ratings for both dermal and inhalation exposure routes. The graphical depictions of confidence levels are appropriate as these are qualitative (high, medium, and low are inappropriate). One SACC member supported the usage of "higher" and "lower" bands with qualitative markings instead of arbitrary high, medium, or low assignments. EPA added a discussion of uncertainties for Modeling Inhalation Exposures with the Tank Truck and Railcar Loading and Unloading Release and Inhalation Exposure Model to Section 4.4.1 of the revised risk evaluation document.
SACC	**SACC COMMENTS:** • Occupational exposure data were often not of adequate quality to support the draft risk evaluation. Measurements are usually reported as non-detectable because monitoring methods are typically keyed to the PEL. Most of the occupational exposure measurements	EPA reviewed information on all aspects of risk evaluations throughout the risk evaluation process, including NIOSH and OSHA data. Multiple NIOSH studies are described in the *Supplemental Information on Releases and Occupational Exposure Assessment*, but were not included in any risk evaluations due to lack of information about the study

	used in the draft risk evaluation occurred in scenarios that are considered well-controlled and for which more data are available. NIOSH and OSHA measurements have been useful for evaluating effects on worker health. • One Committee member suggested that non-detectable values (below detection limit values) are not so much inadequate as insufficiently informative for the task of estimating exposures. • The open burning/open detonation data, which are below the LOD raise the issue of whether large data sets with low results are necessarily superior to smaller data sets with values of the LOD. EPA should clarify how it assesses the relative merits of data set size and quality. Recommendation: Discuss limitations and inadequacies of occupational monitoring data collected to meet PEL standards rather than assess relevant health effects.	(number of samples) and lack of temporal representation (data were collected before the Montreal Protocol and could misrepresent current worker conditions). EPA is aware of the OSHA data and has reviewed over 300 data points for carbon tetrachloride in the OSHA CEHD. The reasons for not using these data are the lack of clarity and data quality on the conditions of use, the date of sampling, and/or inconsistencies in the sample durations and results. Examples included: • The samples reported as non-detects (ND) could be due to the absence of carbon tetrachloride at the site making the dataset not relevant to carbon tetrachloride; • All samples are short-term samples and not representative of full-shift exposures; • Samples were collected prior to the Montreal Protocol and CAA Title VI ban and could include exposures from phased-out uses; • The condition of use could be a non-TSCA use; and • Sample results did not include sample times such that the representativeness of operation and exposures are unknown. Regarding non-detectable values and OB/OD, EPA used established protocols to evaluate occupational exposure data that were reported as below the LOD. This approach has been used consistently across the Risk Evaluations and is summarized in Section 1.4.4.2 of the Supplemental Information on Releases and Occupational Exposure Assessment. For datasets including exposure data that were reported as below the LOD, EPA estimated the exposure

		concentrations for these data, following EPA's Guidelines for Statistical Analysis of Occupational Exposure Data (1994) which recommends using the LOD/$2^{0.5}$ if the geometric standard deviation of the data is less than 3.0 and LOD / 2 if the geometric standard deviation is 3.0 or greater (U.S. EPA, 1994).
SACC	**SACC COMMENTS:** The current PEL for CCl4 was not set based on the health outcomes considered in the draft risk evaluation, but was established many years ago. Lacking an adequate biological basis for past exposure measures, it is important that the risk evaluation emphasize the dependency of the final risk determination on exposure estimates derived from air concentrations measured as below detection limits. Since exposures to ONUs are predicted using worker exposure levels, the same qualifier applies to ONU risk determinations. Because of this, the Committee suggested that the risk evaluation should indicate that all exposure estimates for ONUs are preliminary.	See above response on how exposure data under the LOD were evaluated. In the Section 4.4.1 EPA discussed the dependency of ONU exposure estimates on worker exposure estimates and stated that there is high uncertainty in the exposure estimations.
SACC	**SACC COMMENTS:** A Committee member indicated that the modeling estimates for exposure require additional analysis and discussion in terms of uncertainty.	EPA expanded the discussion of the exposure model uncertainties, as recommended, in Section 4.4.1 of the final risk evaluation document.
SACC	**SACC COMMENTS:** • The risk evaluations continue to focus on the intrinsic quality of the data (*i.e.*, whether exposure sampling and analytical methods were appropriate and fully reported) as the single criteria for acceptability. The risk evaluations have not focused on whether the amount of data available is adequate to derive reliable estimates of exposures for occupational scenarios in a condition of use. The issue of deciding whether there are	EPA indeed considered the number and extent (amount) of exposure data when making risk evaluations and how they affect the data quality. When there is limited information available, EPA acknowledged that there is a greater degree of uncertainty in the exposures and noted that the data may not be widely representative of an industry.

	adequate samples for supporting exposure estimates remains essentially unaddressed. Recommendation: Address directly the issue of how many and what kinds of samples are adequate to quantify exposures for condition of use scenarios.	
26	**PUBLIC COMMENTS:** EPA invokes uncertainty as a basis for excluding exposures, when the scientifically sound and health-protective approach would be to include the exposures and estimate the uncertainty.	EPA did not exclude any occupational exposures due to uncertainties. Rather, decisions to exclude certain workplaces were based on information provided by stakeholders and regulatory bans under the CAA and CPSC.

Human Health Effects		
Charge Question 4.1: Please comment on the reasonableness of the evaluation of human health hazards. Are there any additional carbon tetrachloride specific data and/or other information that should be considered? **Charge Question 4.2:** Please comment on rationale for selection of tumor type for dose response for cancer. **Charge Question 4.3:** Please comment on the appropriateness of using a linear low-dose extrapolation versus a non-linear or threshold approach for assessing low exposures based on the cancer MOA information presented in Section 3.2 and Appendix K. **Charge Question 4.4:** Please comment on the appropriateness of the approaches used for generating PODs for dermal exposures, including the process/equation for extrapolating the cancer slope factor (CSF) and POD for chronic dermal exposures (dermal HED).		
#	**Summary of Comments for Specific Issues Related to Charge Question 4**	**EPA/OPPT Response**
Data used in the acute noncancer assessment		
SACC	**SACC COMMENTS:** • One Committee member expressed concern that inflammatory and immune effects are not adequately discussed in the draft risk evaluation. This represents a large gap in the literature review on CCl4. • There are many studies that use CCl4 as a positive control in animal models of acute liver disease/fibrosis that demonstrate CCl4 has very dramatic pro-inflammatory effects in the liver while simultaneously impairing the function of certain immune cells. • Numerous reports testing the anti-inflammatory	Based on the review of the *on topic* human health references in the systematic review, EPA has concluded that carbon tetrachloride immunological effects were, at least in part, secondary to hepatotoxicity and the process of hepatic repair, which produces adverse effects on T-cell-dependent immunity at doses that are hepatotoxic. A statement on such conclusion was added to the RE document. This conclusion is not based on the extensive number of animal studies in which carbon tetrachloride was used as a positive control to induce a disease state in an animal (*e.g.*,

	activities of various compounds have shown that inflammation drives much of CCl4-induced liver injury. It is unclear why this aspect of CCl4-induced immunotoxicity was not included in the draft risk evaluation. • It was noted that in the supplemental document entitled, Inclusion/Exclusion Criteria for Human Health Hazard Literature, it states that these types of studies are to be included in the draft risk evaluation. This does not seem to have happened for this evaluation. Recommendations: (1) Include discussion on CCl4 effects on inflammatory and immune effects; and (2) explain why studies that evaluated the immune responses induced when CCl4 was used as a positive control for inducing liver inflammation/fibrosis in animals were excluded from data integration during systematic review.	cirrhosis, fibrosis, organ damage: liver, kidney, and others) rather than evaluating adverse effects in animals from carbon tetrachloride exposure . The former type of animal studies was considered off-topic because it provides limited applicability for dose-response in the risk evaluation. Also, sufficient high quality on-topic human health references were identified for carbon tetrachloride. Appendix B in the Problem Formulation and section 1.5 of the final risk evaluation describe the process used to re-screen human health references for prioritizing the literature for applicability in the risk evaluation.
30	**PUBLIC COMMENTS:** Dermal irritation and sensitization should also be listed as likely endpoints of concern. Since there are no studies that evaluate the potential for reproductive effects, this endpoint should NOT be cited on EPA's list.	The Human Health Hazard section and appendix G identify irritation and sensitization as hazards associated with carbon tetrachloride. Although there are no reproductive toxicity studies for carbon tetrachloride, observations of reproductive organ tissues in repeated-dose studies provided some information on the potential reproductive effects of carbon tetrachloride.
30	**PUBLIC COMMENTS:** There is a body of literature on human exposure, both controlled exposure and epidemiologic studies, that provide credible information from which to derive acute PODs and reference values.	Reasonably available information to inform PODs were considered in the systematic review process for this risk evaluation.
32, 43	**PUBLIC COMMENTS:** To determine PODs for estimating risks, EPA relied on a single flawed acute toxicity study (classified unacceptable	Due to the lack of reasonably available dermal studies evaluating non-local or nonlethal effects from exposure to carbon tetrachloride, the RE presents the alternative approach

	in EPA's systematic review) for acute liver effects and extrapolated a human equivalent dose (HED) for chronic effects and carcinogenicity from inhalation studies since no dermal data for these endpoints was available for CCl4.	of extrapolating the acute dermal POD from the estimated chronic dermal POD.
30	**PUBLIC COMMENTS:** The chemical is clearly neurotoxic; this endpoint serves as the basis for the derivation of the acute inhalation exposure POD and benchmark MOE.	The risk evaluation states that the extrapolation of the acute dermal POD from acute inhalation POD was not performed because the critical acute inhalation effects of neurotoxicity are influenced by the accessibility to brain tissue by inhaled carbon tetrachloride.
Data used in the chronic noncancer assessment		
SACC	**SACC COMMENTS:** • Adverse effects of CCl4 on sperm function and morphology have not been addressed in the human health hazards section. • Some reproductive effects have been induced in rodent studies (Smyth et al., 1936; Adams et al., 1952). • The Committee also referenced studies by El-Faras et al. (2016) and Turk et al. (2016). Recommendation: The reproductive toxicity of CCl4 should be addressed and incorporated into the document.	The following statement was added to the RE: "As liver toxicity is identified as the most sensitive effect from repeated inhalation exposures to carbon tetrachloride, OPPT assumes, that similarly to developmental toxicity, potential reproductive effects from carbon tetrachloride exposure are, at worst, secondary to liver toxicity. For instance, effects on the reproductive organs (testes, uterus, etc.) have not been observed in subchronic and chronic animal studies, which suggest that carbon tetrachloride is not likely to be a reproductive toxicant, and that any potential reproductive effects could be only induced, at much higher dose concentrations than liver toxicity." El-Faras et al., (2016) and Türk et al., (2016) studies were not used to reach a conclusion on the developmental toxicity of carbon tetrachloride because as explained above, studies in which carbon tetrachloride was used as a positive control to induce a disease state in an animal (*e.g.*, cirrhosis, fibrosis, organ damage: liver, kidney, and others) rather than evaluating adverse effects in animals from carbon tetrachloride exposure in animals were considered off-topic because they provide limited applicability for dose-response in the risk evaluation. Sufficient high quality on-topic human

		health references were identified for carbon tetrachloride. Appendix B in the Problem Formulation describes the process used to re-screen human health references for prioritizing the literature for applicability in the risk evaluation.
SACC	**SACC COMMENTS:** Recommendation: Effects of CCl4 on the CNS, in rodent studies, should be addressed. • Several P450s are found in a highly regionalized and cell-specific fashion in the brain (Navarro-Mabarak et al., 2018). Furthermore, trans-sulfuration pathways exist there (Vitvitsky et al., 2006). • There are several studies documenting effects of high-level CCl4 exposure on oxidative stress/lipid peroxidation markers in the brain of rodents (Ritesh et al., 2015; Naseem et al., 2014; Al-Olayan et al., 2016).	Acute toxicity studies in humans and animals reported neurotoxic effects of carbon tetrachloride. The systematic review process identified on-topic human health references with human data containing qualitative and quantitative information on the neurotoxicity effects (CNS depression) in humans following acute exposures. Further consideration of the reasonably available animal data was not necessary for the risk evaluation of this endpoint of concern. The metabolic activation of carbon tetrachloride by various P450s found in a highly regionalized and cell-specific fashion in the brain is a consideration in the discussion of the cancer MOA presented in the final risk evaluation.
SACC	**SACC COMMENTS:** One Committee member suggested inclusion of a more comprehensive discussion of possible endocrine effects in the CCl4 risk evaluation. A brief summary of data and references that provide support for an endocrine-related MOA are provided in the committee report including: JBRC (1998), Nagano et al. (2007), Colby (1981), and Narotsky (1997).	Reasonably available information on the endocrine effects of carbon tetrachloride were considered for hazard identification. EPA used the approach described in section **Error! Reference source not found.** of the final risk evaluation to evaluate, extract and integrate carbon tetrachloride's human health hazard and dose-response information
SACC	**SACC COMMENTS:** • No justification is provided for why noncancer endpoints, such as liver fibrosis, are not considered. The risk evaluation should clearly state why the noncancer endpoints, identified and discussed in epidemiological studies, may be less relevant at the low exposures being considered. Recommendation: Include a discussion of noncancer	The identified sensitive endpoint of concern (*i.e.*, fatty changes in the liver, a precursor for liver fibrosis) is based on the principal study for the derivation of the IRIS RfC is (Nagano et al., 2007), which consist of a chronic study using two species and preceded by a 13-week subchronic study. This chronic study is rated of high quality in the systematic review. Other key subchronic inhalation studies of acceptable data quality supporting the identified endpoint of concern are

	health endpoints from epidemiologic studies.	discussed in the RE. The limited number of recent epidemiological studies assessing non-cancer (*i.e.*, Parkinson's disease, autism) endpoints and with acceptable data quality do not show association between exposure and non-cancer hazard effects (see Table 3-1 in RE).
30	**PUBLIC COMMENTS:** There are no studies, human or animal, that focus on characterizing the potential for adverse effects on reproduction or neurodevelopment. For both acute and chronic exposures, at least one developmental toxicity study is needed. For both short-term and chronic exposures, a one- or two-generation reproductive toxicity study is needed. A more systematic evaluation of neurotoxicity and developmental neurotoxicity is needed, since the worker population includes women of childbearing age. Once the risk evaluation is updated to include analyses of any remaining legacy consumer conditions of use, infants and young children become a subpopulation of concern.	The RE indicates that liver toxicity is identified as the most sensitive effect from repeated inhalation exposures to carbon tetrachloride. Based on the available developmental toxicity data, developmental toxicity was not identified as the most sensitive endpoint for inhalation or dermal exposures. OPPT has concluded that potential reproductive effects from carbon tetrachloride exposure are, at worst, secondary to liver toxicity. For instance, effects on the reproductive organs (testes, uterus, etc.) have not been observed in subchronic and chronic animal studies, which suggest that carbon tetrachloride is not likely to be a reproductive toxicant, and that any potential reproductive effects could be only induced, at much higher dose concentrations than liver toxicity.
Data used in the cancer assessment, animal and *in vitro* studies		
SACC, 39	**SACC COMMENTS:** • The observation of significant increases in brain tumors in multiple studies suggests that additional examination of this as a potential target organ is warranted. • However, members of the Committee noted that brain tumors have not been reported in laboratory animal bioassays of CCl4; that a reported association between ambient air concentrations and prevalence of neuroblastomas in one study is not pertinent to this	EPA has conducted a critical and comprehensive evaluation of the epidemiologic studies and a causal analysis with a conclusion. EPA has added that evaluation in Section 3.2.4.2.2. Regarding brain tumors in (Nagano et al., 2007), referred to in the public comment as JBRC, was a study on F334 rats. According to a review of 19 studies of the spontaneous occurrence of astrocytoma in F334/DuCrj rats (Nagatani et al., 2013), the incidence was 0.6% in males and 0.2% in

	issue (since neuroblastomas are not tumors of the brain, contrary to what is stated in the draft risk evaluation); and that the epidemiological studies overall are too few and weak to be conclusive. **PUBLIC COMMENTS:** Neither brain toxicity nor brain tumors have been reported in repeated-dose toxicity studies on CCl4. The rat and mouse 13-week and 2-year inhalation studies by the JBRC did not find any treatment-related effects (cancer or noncancer) associated with the brain or nervous system tissue. Given that EPA considers the JBRC studies to be of high quality and the basis for its cancer risk assessment, it can be concluded that adequate data exist from animal studies to evaluate whether CCl4 exposure is associated with an increased incidence of brain tumors.	females. The review also cites Haseman et al. (1990; 1998) on the occurrence of astrocytoma in F334 rats as less than 1% in both sexes. At a background incidence of 0.4%, 250 rats would need to be in the control group to have an expectation of a single brain tumor. To detect an increased risk of brain tumors would require far more than the standard group size of 50 per dose group. Given the rarity of astrocytoma in F334 rats, it is unclear that the lack of reported effects in (Nagano et al., 2007) conflicts with the epidemiologic evidence.
SACC	**SACC COMMENTS:** One Committee member noted that the draft risk evaluation did not appear to use *in vitro* studies. Another member noted that caution should be used when evaluating *in vitro* CCl4 data given its volatility and that common diluents used for *in vitro* studies (methanol, ethanol, dimethyl sulfoxide [DMSO]) were competitive inhibitors of CYP2E1 and may interfere with CCl4 bioactivation in those systems.	*In vitro* studies were evaluated by EPA when synthesizing and integrating evidence for human health hazards. EPA considered quality, consistency, relevancy, coherence and biological plausibility as specified in *Application of Systematic Review in TSCA Risk Evaluations*.
39	**PUBLIC COMMENTS:** The animal toxicity data on CCl4 do not support brain tumors being a health concern. The Ritash et al. (2015) study used only a single oral dose, so information on dose-response is lacking, including whether the effects in the brain can occur at lower doses than in the liver. Nevertheless, the acute oral dose is orders of magnitude higher than doses that are expected to occur from realistic	Site concordance of tumors can be important evidence, however site concordance is not always assumed. Brain tumors are rare in both people and in rats. In F334 rats the incidence is 0.4-0.5% (additional detail in response to SACC comment #39). The lack of reported effects in animal studies may not support the association reported in multiple epidemiologic studies, but they do not refute those observations.

	human exposure to CCl4, and therefore, the study is of questionable relevance to EPA's risk evaluation.	
39	**PUBLIC COMMENTS:** The JBRC rodent inhalation bioassays on which the IUR for CCl4 is based were not adequately evaluated by EPA in the risk evaluation, nor were new scientific data included in the risk evaluation that provide important evidence for a cytotoxic-proliferative MOA of CCl4 at low doses.	The JBRC rodent inhalation bioassays are described in (Nagano et al., 2007), which was found to have high data quality in the systematic review for this risk evaluation. The findings from the JBRC bioassays are used for cancer MOA and cancer dose-response in both the IRIS assessment and this risk evaluation.
39	**PUBLIC COMMENTS:** Historical control data in Crj:BDF1 mice from 20 studies at JBRC suggests that the incidence of liver adenomas was unusually low in control mice in the CCl4 study, thus exaggerating the statistical difference between the 5 ppm females and the controls. The wide range in the historical control range for liver adenomas may also indicate that background rates for these tumors are highly variable.	The incidence of benign adrenal pheochromocytomas was increased in males at 25 or 125 ppm and females at 125 ppm. The incidences of hepatocellular adenomas and carcinomas were elevated in both sexes at ≥25 ppm. At 5 ppm, the incidence of liver adenomas in female mice (8/49 or 16%) was statistically significantly elevated compared to the concurrent control group and exceeded the historical control range (2–10%). The possibility that the increased incidence of liver adenomas in the 5 ppm female mice is an experimental artifact from an unusually low incidence of liver adenomas in the control mice was explored by comparing the incidence of liver adenomas in the study controls to the historical laboratory control data. The incidence of liver tumors in control mice (18% in males and 4% in females for hepatocellular adenoma and 34% in males and 4% in females for hepatocellular carcinoma) were similar to historical control data for liver tumors in Crj:BDF1 mice in 20 studies at the JBRC (Katagiri et al., 1998). Thus, the historical control data from the laboratory seems to strengthen the conclusion that the low dose female adenoma result is likely compound related.
45	**PUBLIC COMMENTS:** There is a considerable degree of variability in the rate of	The incidence of benign adrenal pheochromocytomas was increased in males at 25 or 125 ppm and females at 125 ppm.

	liver adenomas in control BDF1 mice. A separate analysis of spontaneous liver tumors conducted by JRBC (1998) reported a relatively high incidence of hepatocellular adenomas in both sexes of BDF1 mice: specifically, up to 8% of females and 30% of males. Similarly, Yamate et al. (1990) investigated the rate of tumorigenesis in BDF1 mice allowed to live out their lifespan and found that spontaneous hepatocellular adenomas were common in both male and female mice of this strain (7/50 males [14%] and 6/50 females [12%]). EPA should acknowledge both the high rate and the variability in the rate of spontaneous liver adenomas (and carcinomas) in this strain of mice in its discussions of Nagano et al. (2007) and of the plausible MOAs for the carcinogenicity of CCl4.	The incidences of hepatocellular adenomas and carcinomas were elevated in both sexes at ≥25 ppm. At 5 ppm, the incidence of liver adenomas in female mice (8/49 or 16%) was statistically significantly elevated compared to the concurrent control group and exceeded the historical control range (2–10%). The possibility that the increased incidence of liver adenomas in the 5 ppm female mice is an experimental artifact from an unusually low incidence of liver adenomas in the control mice was explored by comparing the incidence of liver adenomas in the study controls to the historical laboratory control data. The incidence of liver tumors in control mice (18% in males and 4% in females for hepatocellular adenoma and 34% in males and 4% in females for hepatocellular carcinoma) were similar to historical control data for liver tumors in Crj:BDF1 mice in 20 studies at the Japan Bioassay Research Center JBRC (Katagiri et al., 1998). Thus, the historical control data from the laboratory seems to strengthen the conclusion that the low dose female adenoma result is likely compound related.
39	**PUBLIC COMMENTS:** While liver adenomas were increased in the 5 ppm-exposed female mice in the absence of liver toxicity, this increase was not statistically significant using the level of significance ($p<0.01$) used by NTP and others; this increase may been artifactual due to an unusually low incidence of liver adenomas in the control mice. Therefore, 5 ppm should be considered a no-observed-effect-concentration NOEC for both liver toxicity and liver cancer.	The significance of the 8/49 adenomas in the 5ppm dose female group as compared with 2/50 in the matched controls is P = 0.05, which is statistically significant in the IRIS assessments and TSCA risk evaluations. The study authors published a report on the historical control incidence in these mice in their lab. (Katagiri et al., 1998) reports on spontaneous lesions in the BDF1 mice in 10 bioassays they had conducted. The number of female mouse adenomas ranged from 1/50 to 4/50, with an overall incidence of 4.4% as compared with the 8/49=16% observed in the low dose carbon tetrachloride females. Thus, the

		historical control data from the lab seems to strengthen the conclusion that the low dose female adenoma result is likely compound related.
30	**PUBLIC COMMENTS:** The Agency should use its enhanced testing authority in the "new" TSCA to require submission of the studies of reproduction, genotoxicity, developmental neurotoxicity, and others relevant to MOA/AOP characterization. For chronic exposures, studies that would adequately test for carcinogenic potential by the relevant route(s) of exposure or that could be extrapolated to those routes of exposure are needed.	EPA had sufficient information to complete the carbon tetrachloride risk evaluation using a weight of scientific evidence approach. EPA selected the first 10 chemicals for risk evaluation based in part on its assessment that these chemicals could be assessed without the need for regulatory information collection or development. When preparing this risk evaluation, EPA obtained and considered reasonably available information, defined as information that EPA possesses, or can reasonably obtain and synthesize for use in risk evaluations, considering the deadlines for completing the evaluation. The JBRC rodent inhalation bioassays described in (Nagano et al., 2007), were found to be high quality inhalation bioassays in the systematic review for this risk evaluation. The lack of chronic dermal studies is acknowledged in the risk evaluation as a key source of uncertainty.
Data used in the cancer assessment, epidemiological studies		
SACC, 23, 32, 33, 39, 43, 45	**SACC COMMENTS:** • The risk evaluation should include the Heineman et al. (1994) study as well as other epidemiological studies on CCl4 that may have investigated the occurrence of gliomas, brain tumors, and other types of cancer. Standard epidemiological approaches for extracting the data should be employed with the full range of risk estimates presented. • The Committee noted that Heineman et al. (1994) reported that after adjusting for co-exposure to other chlorinated aliphatic hydrocarbons, the association of CCl4 to brain cancer was no longer statistically	EPA has added a critical and comprehensive evaluation of the epidemiologic studies of carbon tetrachloride and brain cancer (including (Heineman et al., 1994)) and a synthesis of the available evidence for carcinogenicity that takes into account the considerable research in animals showing that carbon tetrachloride can pass through the blood-brain barrier, is rapidly absorbed by the brain and liver, causes oxidative stress in the brain, and is metabolized in the brain. Evaluation of the epidemiologic studies of carbon tetrachloride and brain cancer included application of the Bradford-Hill considerations as well as discussion of any potential biases and the evidence integration weighed that evidence across the

	significant and the odds ratio (OR) at the highest level of exposure was actually decreased from the medium exposure level. • One Committee member recommended that citation and discussion of the older epidemiologic studies be added to Tables 3-7 and 3-8 of the draft risk evaluation. Though the Committee member understands that the studies were part of the previous evaluation, they appear to add weight of evidence for the overall evaluation of the chemical. Recommendations: (1) A critical and more comprehensive evaluation of the reported associations between CCl4 and brain cancer is needed; and (2) expand the discussion of the Heineman et al. (1994) study. Recommendation: Revise the table listing epidemiologic studies per the example given in the SACC report Table 2, and apply Bradford-Hill criteria in assessing study strengths. Endpoints to consider should be chosen *a priori*, and then reported uniformly across studies. **PUBLIC COMMENT PART 1: Conclusions from brain cancer studies are not reliable** Considering the risk of bias, lack of consistency, and high contribution of chance and confounding, it was concluded that the five studies by Nelson et al. (2012), Neta et al. (2012), Heck et al. (2013), Ruder et al. (2013), and Heineman et al. (1994) do not show an increased risk of brain and nervous system tumors due to CCl4 exposure. While EPA reviewed each study across six domains with respect to quality and risk of bias, there was no discussion regarding causal inference or WOE across studies. It is	body of the literature regarding causal inference. EPA has added that evaluation in Section 3.2.4.2.2. The four epidemiologic studies of brain cancer are reviewed and discussed in section 3.3.4.2 of the final risk evaluation . Findings from the newer epidemiologic data on carcinogenicity have been included, qualitatively, in the cancer MOA and dose-response conclusions.

	important to note in these small epidemiology studies of rare diseases and uncommon exposures that artificially high risk estimates can occur from random variability, resulting is a phenomenon of effect size magnification. The results may be statistically significant but with very wide CIs that indicate imprecision. The lack of precision in low powered studies may be quantified by calculating the ratio of the upper and lower confidence limits (Poole, 2001). The NTP OHAT guidelines deem the risk of bias to be "very serious" if the CI ratio is ≥10. Other reviewers have considered the measures to be precise if the CI ratio is below 4 (Schinasi and Leon, 2014). This imprecision is seen in all five of the epidemiology studies, with the exception of the case-control study by Ruder et al. (2013), which showed no association between brain tumors and CCl4 exposures. **PUBLIC COMMENT PART 2: Conclusions from brain cancer studies are reliable** Section 3.2.3.3.2 (Carcinogenicity) provides very little discussion of the body of epidemiological studies and provides no discussion of the implications of recent studies of nervous system cancers (Heck et al., 2013; Nelson et al., 2012; Neta et al., 2012; Ruder et al., 2013). Given their high quality, significant results, and consistency with each other, the three positive brain cancer studies (Nelson et al., 2012, Neta et al., 2012, Heck et al., 2013) should be used in assessing CCl4 cancer risks (the one study by Ruder et al. that failed to identify a cancer risk should not be relied upon, as it lacked detailed information on exposures, and instead assumed that workplace levels were within the ranges reported in the	

	literature, making it too limited to support a no-risk finding). Although describing these studies, the draft evaluation does not include them in its analysis of the weight of the scientific evidence for carcinogenicity, its determination of a cancer inhalation unit risk or its risk estimations for cancer effects. Based on these studies, EPA should classify CCl4 as "Carcinogenic to Humans" under its cancer risk assessment guidelines because "there is convincing epidemiologic evidence of a causal association between human exposure and cancer." **PUBLIC COMMENT PART 3: Further comments on Heck et al. 2013** EPA incorrectly described Heck et al. (2013) as a study of brain cancer, but it was actually of neuroblastomas, a childhood cancer arising from cells that form the sympathetic nervous system, which is not the brain. This should not be considered as a brain cancer with the other studies of adult occupational exposure to CCl4. Evidence is inconclusive due to small number of exposed cases, poor precision in risk estimates, and low-quality exposure assessment. Limitations include: (1) the exposure assessment was low quality and was inferred based only upon residence at birth; (2) methods for calculating the mean concentrations were vague; (3) no information was provided for the actual concentrations of CCl4 (and other pollutants) over time or by location; (4) sensitivity analysis would have added confidence to the results; and (5) analytic techniques are available to model the impact of greater or lesser mobility upon the exposure-outcome	

	models. Strengths include: (1) record linkage studies are not subject to participation rate and recall bias; (2) exposure metrics were based on actual stationary monitors, omitting the need for self-reporting of exposure and/or job history; and (3) with the use of monitors, concentrations were specific to CCl4 (versus chlorinated solvents). WOE: Because of limitations in exposure assessment, it is likely that misclassification occurred. It is unknown how the children born in the 1990-1998 period, for whom only zip code was available, were included in these analyses. Heck et al. (2013) is limited by its ecological design in which exposure was estimated relatively crudely; specifically, using ambient air pollution monitoring stations and classified according to distance from these monitors. Rates of cancers may vary geographically due to differences in socioeconomic status, underlying prevalence of other risk factors, and so forth; therefore, the cause(s) of any differences in cancer rates cannot be elucidated. **PUBLIC COMMENT PART 4: Further comments on Nelson et al. 2012** The evidence from Nelson et al. (2012) is inconclusive due to small number of exposed cases, poor precision in risk estimates, and low-quality exposure assessment. Limitations include that the statistical power was low due to the small number of glioblastoma multiforme cases (N = 9) and only two cases had probable exposure to CCl4. Strengths include that data were collected prospectively before the subjects were ill, which reduces the problem of information bias and low participation rates. WOE: Because of limitations in exposure assessment, it is likely that misclassification occurred. In addition to poor	

	exposure information, this study had very few cases, resulting in incidence rates and risk measures with a large magnitude of uncertainty, evidenced by wide CIs. **PUBLIC COMMENTS Part 4: Further comment on Neta et al. (2012)** Neta et al. (2012): This study of glioma and meningioma was inconclusive. The risk estimates when comparing high to low exposed are statistically significant but imprecise. No association was observed for meningioma and CCl4. Limitations include: (1) differential information bias may have occurred from the cases being more motivated to contribute detailed occupational information; and (2) exposure to CCl4 was based upon the job history and likely affected by recall bias. Strengths include that cases were identified and enrolled in the study very quickly; the study was of incident cases not deaths, reducing the number of proxy interviews; and the authors conducted sensitivity analyses to test various hypotheses and reran different statistical models. WOE: The authors conducted analyses in two ways: one using unexposed as the referent and another using low exposed as a referent. Their rationale was provided that "unexposed persons may be substantially different from exposed persons in ways that cannot be adjusted for in our analysis." However, they do not discuss how or why this may occur. **PUBLIC COMMENTS Part 5: Further comment on Ruder et al. (2013)** Ruder et al. (2013): No increased risk was observed for gliomas and exposure to CCl4. These results were not statistically significant, but the CI ratio was <4, indicating precision. Limitations include: (1) all exposure information	

	was collected retrospectively, with a high proportion from proxies; (2) the focus of the study was on agricultural exposures and the participants may have forgotten relevant exposed jobs.; (3) the estimates of job-based exposures to CCl4 were based upon models reported in the literature; and (4) as the authors noted, they were unable to determine if their study participants' experiences were consistent with these estimates. Strengths included: (1) the study was based upon confirmed incident cases of glioma (versus cases from death certificates); (2) the authors stratified their results by respondent type (*i.e.*, proxy) so that information bias, if present, could be quantified; (3) there were a large number of exposed cases permitting sufficient statistical power to evaluate solvent exposures; and (4) genotypes for glutathione-S-transferase were evaluated to test for genetic susceptibility. WOE: Adequate design, high outcome ascertainment and a specific exposure metric. No increase in exposure to CCl4 was observed in any analysis of glioma. **PUBLIC COMMENTS PART 6: further discussion of Heineman et al. 1994** Heineman et al. (1994): There is no increased risk of astrocytic brain cancer when limited to subjects with high probability of exposure (odds ratio = 0.8) and when controlling for other solvents. Limitations include: (1) all of the exposure and lifestyle information was based upon interviews with a proxy, which is likely to be incorrect recall especially for jobs in the distance past; (2) the data available on each job lacked specificity for unique solvents and poor temporal detail; and (3) the overall participation was poor, which may introduce bias if participation was influenced by perception of exposure. Strengths include	

	reporting by probability of use, which permits the reader to evaluate results for the group with the highest confidence of exposure. WOE: The sample size is greatly reduced from "ever" exposed to "high probability" of exposed. Most analyses show no excess risk and are not statistically significant.	
Methods used in the noncancer assessment: evidence synthesis and POD selection		
SACC	**SACC COMMENTS:** Recommendation: Improve the discussion and include more details about the selection and derivation of the PODs (including calculations where possible). • For example, in Section 3.2.5.1.2 on p. 128 of the draft risk evaluation, why was the 25 parts per million (ppm) from the rat data in the Nagano study selected to derive the POD rather than the mouse data from the same study, or why weren't the eosinophilic granules seen in the rats at 5 ppm used? • More information is needed on the calculation of the HECs and the adjustments to convert from continuous exposure to the 8- and 12-hour occupational exposures. • Which $BMDL_{10}$ calculation was used and how was it used to derive the 14.3 mg/m^3 value? • Most of the $BMDL_{10}$ outcomes from the modeling in the appendix appear in µmol/L units, which is very different from most EPA assessments. Similarly, it would help the reader if the actual calculations were provided in the footnote of Table 3-14 to illustrate how the occupational exposure levels were calculated. • The basis for all of the critical PODs, especially those in Table 3-17, should be shown.	The following language was added to Section 3.2.5.1.2: "Fatty change in the liver of rats was selected as the endpoint for dose-response analysis because this histopathologic lesion, which is indicative of cellular damage was a more sensitive endpoint than other histopathologic changes that were also observed in rats exposed to 25 ppm from the (Nagano et al., 2007) study. The only histopathological change observed in the 5 ppm group in the chronic rat study is an increase in eosinophilic granules in the nasal cavity of the female rats. This histopathological change is not considered an adverse effect by itself because it is not accompanied by other adverse effects in the nasal cavity. Furthermore, while severe renal and hepatic effects are observed in the high-exposure group, the nasal lesion is only of moderate severity in such exposure group." The dose response analysis included the use of the PBPK model and BMD modeling methodology used in the IRIS Toxicological Review (U.S. EPA, 2010) to estimate internal doses and analyze the relationship between the estimated internal doses and fatty change (*i.e.*, response). The resulting BMDL values were converted to estimates of equivalent HECs by applying a human PBPK model. Estimated values for HECs corresponding to BMDL10 values for fatty changes of the liver for alternative values of V_{maxC} in the rat and

		human are presented in in Tables 5-6 and 5-7 of the IRIS Toxicological Review (U.S. EPA, 2010). A human V_{maxC} estimated from in vitro human data can reasonably be presumed to be more relevant than a human V_{maxC} based entirely on rodent data. Because the MOA for carbon tetrachloride-induced hepatotoxicity involves metabolism to reactive metabolites in the liver, HECs based on the mean rate of metabolism in the liver dose metric is the most proximate to the critical effect. The resulting $BMCL_{10[HEC]}$ based on data for the male rat is 14.3 mg/m3 for continuous exposures. Language in Section 3.2.5.2.2 already states that the $BMDL_{10}$ value for continuous exposures was extrapolated to shorter exposure durations using the equation $Cn \times t = k$, where an empirical value of n was determined to be 2.5 on the basis of rat lethality data (Ten Berge et al., 1986) This language was modified as follows: "BMDL10 value for continuous exposures was extrapolated to shorter occupational exposure durations (8-hr/day and 12 hr/day) using the equation $Cn \times t = k$, where an empirical value of n was determined to be 2.5 on the basis of rat lethality data (Ten Berge et al., 1986). Further information on this temporal scaling equation can be found in (NRC, 2014)." The column 'Basis for Selection' in Table 3-17 was also updated.
SACC	**SACC COMMENTS:** Some Committee members noted that the HEC computed in the draft risk evaluation is below doses observed in the original animal study and similarly below the current PEL. The basis for the chronic inhalation POD was set	The chronic POD for inhalation exposures is based on a study observing increased fatty changes in rodent livers (Nagano et al., 2007). The lowest exposure concentration (5 ppm) in the 104-weeks inhalation study with F344/DuCrj rats (Nagano et al., 2007) was considered a NOAEC based

	using the NOAEC for liver cancer of 5 ppm based on the Nagano et al. (2007b) rodent study (p. 130, lines 4176-4178). More data are needed to validate use of such a low HEC value. Such data might be obtained by NTP via a 13-week inhalation study using 4-5 concentrations between 50 ppb and 5 ppm. Barring this study, the risk characterization in the risk evaluation should be labeled as preliminary, primarily due to this low-dose extrapolation.	on liver and kidney toxicity at ≥ 25 ppm. Interpretation of the observed proteinuria and the renal lesions in the F344 rat is difficult because this strain has a high spontaneous incidence of renal lesions. Increases in the incidence and severity of nonneoplastic liver lesions (fatty change, fibrosis, cirrhosis) were seen at 25 and 125 ppm in both males and females. The HEC (in mg/m^3) consisting of $BMDL_{10}$ for fatty changes of the liver of 14.3 mg/m^3 for continuous exposures was estimated using a PBPK model in the peer-reviewed IRIS Toxicological Review for Carbon Tetrachloride.
SACC	**SACC COMMENTS:** • A Committee member commented that they would like to see more discussion as to why a NOAEL of 5 ppm is used when there were effects seen in JBRC (1998) (*e.g.*, spleen, urine analysis, white blood cell count) at 5 ppm that do not seem to be reported in Nagano et al. (2007a). This Committee member suggested that these observed effects could inform levels impacting developmental neurotoxicity and immune effects. • Despite the many changes observed in the JBRC studies at the lowest doses, the draft risk evaluation reports lowest and mid doses as NOAELs for key endpoints in Appendix H and line 4175 that are higher.	The systematic review for this risk evaluation identified (Nagano et al., 2007) as a high quality study. (Nagano et al., 2007) is based in JBRC study described in the JBRC, 1998 reference. The JBRC 1998 reference was specifically evaluated in the peer-reviewed IRIS Toxicological review for Carbon Tetrachloride. IRIS evaluation of JBRC 1998 did not identify adverse immune effects at non-hepatotoxic doses.
SACC	**SACC COMMENTS:** Recommendation: The toxicokinetics discussion should be updated and expanded, particularly on the influence of exposure route on systemic disposition and effects, as well as inter- and intra-species differences in metabolic activation and susceptibility. • It was noted on lines 4085-4091 that the utility of the	The final risk evaluation contains the following statement explaining the limited utility of the oral study for risk characterization: "oral exposures to carbon tetrachloride undergo first-pass metabolism in the liver, the organ with the highest concentration of CYP2E1 enzymes involved in the generation of carbon tetrachloride's toxic metabolites. This major difference in the metabolism of carbon tetrachloride

	oral developmental study of Narotsky et al. (1997) was limited; however, the reason was not clearly described, namely that first-pass hepatic metabolism following ingestion reduced the amount of CCl4 reaching the systemic (arterial) circulation and extra hepatic organs. With low dose oral exposures, the liver and lungs, acting in concert, eliminated/removed virtually all CCl4 and other VOCs before they enter the systemic circulation. High oral doses, however, can exceed the uptake and metabolic capacity of the liver systemic circulation. • The findings of Sanzgiri et al. (1997) are applicable here. They characterized the influence of route and rate of administration of CCl4 on blood and tissue levels of CCl4 in rats. Presystemic elimination of CCl4 can be protective of extrahepatic organs, but the liver often "bears the brunt" of adverse effects (Sanzgiri et al., 1995). • There are no descriptions in Section 3.2.2 on toxicokinetics of the time-course of CCl4 or its key metabolites, for use in understanding the chronicity of adverse effects of single and multiple exposures. The Committee suggests using data from Kim et al. (1990) and Rao and Recknagel (1968, 1969). • The Committee agreed that it would be worthwhile to expand the description of CCl4 metabolism, and to link the chemical's bioactivation to its MOA. The Committee noted that there was an excellent publication by Slater (1987) describing biochemical reactions and effects of the chloromethyl peroxyl radical and subsequent products of lipid peroxidation. • The experimental protocol of an unpublished study by Benson and Springer (1999) is described on pp. 107	between oral and inhalation routes of exposure limits the usefulness of extrapolating a developmental inhalation POD from the oral developmental study, given that different developmental toxicity processes may be involved between the two routes of exposure." The Toxicokinetics section was expanded to include the following language: The toxicokinetics of carbon tetrachloride have been comprehensively described in previous toxicological assessments (see **Error! Reference source not found.**). In summary, the IRIS assessment describes that carbon tetrachloride is "rapidly absorbed by any route of exposure." However, it is noted that dermally absorbed fraction would be "negligible for exposures to carbon tetrachloride vapor (Mccollister et al., 1951)." Once absorbed, carbon tetrachloride is widely distributed among tissues, especially those with high lipid content, reaching peak concentrations in <1–6 hours, depending on exposure concentration or dose. Animal studies show that volatile metabolites are released in exhaled air, whereas nonvolatile metabolites are excreted in feces and to a lesser degree, in urine. Findings from (Sanzgiri and Bruckner, 1997), in which tissue distribution of inhaled carbon tetrachloride was compared to the equivalent oral dose show that maximal levels in fat were considerably in excess of the maximal levels in other tissues, regardless of route of exposure. Among tissues other than fat, distribution kinetics were generally similar for the tissues, except that maximal levels were higher and attained

	and 108 of the draft risk evaluation, but relatively few of their findings or conclusions are mentioned. Derivation of human metabolic rate constants was mentioned, but no results were provided. Was any information obtained to assess the existence of genotoxic versus non-genotoxic mechanisms of liver tumors? Thrall et al. (2000) did report the following rank order of CCl4 metabolism: hamster > mouse > rat > human.	more quickly in the liver than in other tissues following bolus oral administration. The metabolism of carbon tetrachloride has been extensively studied in *in vivo* and *in vitro* mammalian systems. Carbon tetrachloride is metabolized in the body, primarily by the liver, but also in the kidney, lung, and other tissues containing CYP450. Based on reasonably available information, the initial step in biotransformation of carbon tetrachloride is reductive dehalogenation: reductive cleavage of one carbon-chlorine bond to yield chloride ion and the trichloromethyl radical. Biotransformation of carbon tetrachloride to reactive metabolites, including the trichloromethyl radical, is hypothesized to be a key event in the toxicity of carbon tetrachloride. The fate of the trichloromethyl radical depends on the availability of oxygen and includes several alternative pathways for anaerobic or aerobic conditions. Anaerobic dimerization forms hexachloroethane, while aerobic trapping by oxygen forms a trichloromethyl peroxy radical. The trichloromethyl peroxy radical is the primary initiator of lipid peroxidation that occurs from exposure to carbon tetrachloride (Rao and Recknagel, 1969) Cytochromes CYP2E1 and CYP2B, the primary enzymes responsible for biotransformation of carbon tetrachloride in rodents, were measured in all exposed and control animals in the metabolic studies by (Benson and Springer, 1999). In all species, microsomal measurement of these enzymes indicated that while enzyme induction increased several fold as dose increased, catalytic activity was not significantly altered. In addition, the rate of carbon tetrachloride metabolism was measured in rat, mouse and hamster species.

		The metabolic rate of carbon tetrachloride did not vary more than 2-fold between the three species(Benson and Springer, 1999). (Thrall et al., 2000) and (Benson and Springer, 1999) used *in vitro* data on metabolism of carbon tetrachloride by human liver microsomes and in vitro and in vivo rodent data, to estimate the in vivo human metabolic rate constants. Those rate constants were used by the IRIS Program for interspecies extrapolation (*i.e.*, rat-to-human, mouse-to-human) and route-to-route extrapolation of carbon tetrachloride inhalation dosimetry using a human PBPK model, which has been described in (Paustenbach et al., 1988)), (Thrall et al., 2000) and (Benson and Springer, 1999).
Methods used in the cancer assessment: selection of tumor type, MOA, POD, and IUR calculation		
SACC, 39	**SACC COMMENTS:** • In the JBRC (1998) inhalation cancer bioassay, there were increased adrenal, endometrium, ovary, and thyroid (as well as pancreas, spleen, and subcutis) tumors reported at low and mid doses in female rats. While many of these did not reach statistical significance, taken together, they are notable, and it would be a more complete presentation to include a summary of these findings in the risk evaluation. • These endocrine tumors are consistent with evidence of an endocrine MOA for some noncancer and cancer endpoints observed with CCl4 and further discussion on this point would contribute to discussion of cancer MOA. Recommendation: Include a summary table of tumors observed in endocrine-associated tissues in the JBRC (1998) inhalation study, particularly for female rats, and	EPA relies on current agency guidance and risk assessment practice for developing cancer assessments in TSCA risk evaluations. Adding up different type of tumors to reach statistical significance or use of the Haseman Rule are not in agreement with current Agency guidelines for cancer assessment. One of the general considerations for MOA analysis in the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005) for analyzing an agent's influence in the development of tumors is the consideration of an agent working by more than one MOA at different sites and at the same tumor site. Therefore, the cancer MOA cannot be generalized to other tissues or cell types without additional analyses.

	include a discussion of their significance. **PUBLIC COMMENTS:** The NTP uses what is known as the "Haseman Rule," which tests the significant differences in tumor incidence between the control and dose groups at 0.05 for rare tumors and at 0.01 for common tumors. Based on the "Haseman Rule," the increased incidence of liver adenomas in the 5 ppm female mice is not statistically significant at $p<0.01$ and should therefore not be considered treatment-related.	
SACC	**SACC COMMENTS:** Recommendation: Major points about genotoxicity of CCl4 should be brought forward from Appendix I, including overall conclusions reached about strengths, weaknesses, and limitations of existing studies, WOE, and data needs. • The SACC report offers a detailed discussion of a proposed MOA, including noting that many studies have demonstrated that CCl4 impairs the immune system, and that immune suppression promotes tumor growth. • One Committee member recommended that EPA better explain why genomics, proteomics, genotoxicity, indirect genotoxicity, changes in gene expression, or messenger ribonucleic acid (mRNA) levels were excluded while evaluating CCl4 MOA studies of *in vitro* models.	Major points about genotoxicity have been brought forward from Appendix I. EPA considered the genotoxicity, indirect genotoxicity, changes in gene expression studies while evaluating carbon tetrachloride MOA studies of in vitro models. Those studies were used to identify the key events in the MOA. Other studies (*i.e.*, proteomics and genomics) that provided more detailed mechanistic information within each key event were considered off topic. Information on the criteria for determination of on topic and off topic studies can be found in section 1.5.1 of the final risk evaluation.
SACC, 39	**SACC COMMENTS:** • Specific molecular and cellular mechanisms through which CCl4 exerts its toxicity have been thoroughly investigated and this deep knowledge of the mechanisms of action of CCl4 should be carried	The discussion on the carcinogenicity MOA has been expanded in the final risk evaluation. However, Khan and Younus (2011) is an *in vitro* study in which carbon tetrachloride was used as a positive control to induce a disease state. This type of study was considered off-topic in

	through to the human health risk assessment. • Key steps occurring in both liver and adrenal gland tumor formation should be compared. A diligent effort should be made to update the literature review in this area as there are likely to be relevant studies that have been published in the 10-15 years since the IRIS document was written. • For example, a study by Khan and Younis (2011) describes oxidative damage occurring in the adrenal gland following CCl4 administration. Also, the U.S. EPA (2010) evaluation missed key studies, such as Slater (1987). Recommendation: Expand the discussion of CCl4's MOA for carcinogenicity in both the liver and adrenal gland. **PUBLIC COMMENTS:** Below are several key points suggesting similar low-dose threshold MOAs for both liver and adrenal medulla tumors: • Adrenal medulla cells have the same basic cell structure as liver cells. • CCl4 is expected to be metabolized to trichloromethyl and trichloromethyl peroxy radical metabolites in the endoplasmic reticulum. Reactive CCl4 radical mechanisms in adrenal medulla cells are expected to be similar to liver cells. • Antioxidant defense mechanisms in adrenal medulla cells are expected to be similar to liver cells. Mutagenic MOA for tumors is not supported by genotoxicity data.	the systematic review because it provides limited applicability for dose-response in the risk evaluation. In addition, sufficient high quality on-topic human health references were identified for carbon tetrachloride. Appendix B in the Problem Formulation describes the process used to re-screen human health references for prioritizing the literature for applicability in the risk evaluation. Furthermore, the findings from Khan and Younus (2011) show that carbon tetrachloride does induce oxidative stress. This conclusion has been reached in the IRIS assessment and this risk evaluation without the need of that study. The final risk evaluation indicates that metabolism of carbon tetrachloride leads to the production of free peroxy radicals which induce oxidative stress with, which can damage proteins, DNA and lipids. The IRIS assessment indicates that in vitro studies by (Colby et al., 1994) showed that preincubation of adrenal microsomes with 1-aminobenzotriazole, a CYP450 suicide inhibitor, prevented the effects of carbon tetrachloride on lipid peroxidation and covalent binding. Nevertheless, there is not sufficient information to elucidate the key events for cancer induction in the adrenal gland and astrocytic brain tissues. Slater 1987 consist of a lecture transcript. The studies on carbon tetrachloride cited in the lecture were evaluated in the IRIS assessment, which is one of the assessments considered in the systematic review for this risk evaluation.
SACC	**SACC COMMENTS:** Recommendation: The contribution of inhibition of immune function to an indirect carcinogenic MOA should	Based on the review of the *on topic* human health references in the systematic review, EPA has concluded that carbon tetrachloride immunological effects were, at least in part,

	be discussed.	secondary to hepatotoxicity and the process of hepatic repair, which produces adverse effects on T-cell-dependent immunity at doses that are hepatotoxic. However, elucidation of the exact mechanism by which carbon tetrachloride induces tumors is outside the scope of this risk evaluation.
SACC, 30, 31, 39, 43, 45	**SACC COMMENTS: points against low-dose linear mechanism of action** • Although the draft risk evaluation claims to have "Evaluated the weight of the scientific evidence based on the available human health hazard data for carbon tetrachloride," the Committee noted that convincing support for this claim is lacking. • In particular, the draft risk evaluation refers repeatedly to a concern that low-level exposures to CCl4 may somehow act through genotoxic mechanisms (evidence for this notwithstanding); indeed, this concern is its underlying justification for using the "default" approach of applying a linearized model to the tumor mouse bioassay data in order to predict low-dose cancer risk. But the WOE clearly indicates that any genotoxicity caused by CCl4 can occur only at exceedingly high levels of exposure, and is caused not by CCl4 directly, but only indirectly after high levels of lipid peroxide byproducts (such as reactive aldehydes) have accumulated intracellularly (see, for example, Slater, 1987; MAK, 2000; Weber et al., 2003; Eastmond, 2008; Hernandez et al., 2009; Borgert et al., 2015). No support is provided for EPA's designation of an "alternate MOA" that combines cytotoxic mechanisms at relatively high CCl4 doses with "alternate, non-cytotoxic mechanisms" at lower doses.	The evidence on cancer MOA has been revisited and expanded for liver, adrenal and brain tumors. In addition, the key events for the liver tumors MOA and uncertainties of alternate MOAs are presented in appendices of the final risk evaluation. The cancer assessment relies in the 2010 IRIS Toxicological Review of Carbon Tetrachloride(U.S. EPA, 2010) findings, newer epidemiological studies presenting additional evidence of an association between carbon tetrachloride exposure and neuroblastomas (adrenal gland tumors in infants) and brain cancers and alternate MOA information. The final risk evaluation includes evaluation of the available carcinogenicity studies and MOA information in support of evaluating the potential cancer risk for carbon tetrachloride. MOA information on carbon tetrachloride has been evaluated in the context of EPA's "MOA framework" as presented in EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), (see Chapter 2.4 of EPA's 2005 cancer guidelines). The new epidemiological information provides evidence on carbon tetrachloride carcinogenicity in humans when considered with the site concordance with pheochromocytomas (adrenal gland tumors) in mice and other evidence of hepatic tumors in multiple species. The key events underlying the MOA for induction of liver

	• What is meant by an "alternate non-cytotoxic mechanism" (p. 124, line 4005)? This appears to be speculation that something must be occurring to produce an increased incidence in liver adenomas in the female mice dosed at 5 ppm. • Consideration should be given to the possibility that this was a chance occurrence in a single study. The historical incidence of this benign tumor in control Crj:BDF1 mice is as high as 10%. • Had 3 of 50 control females exhibited liver adenoma in this particular experiment, the difference between them and the 5 ppm dose group would not have been statistically significant. There was no increase in liver carcinoma incidence in the females dosed at 5 ppm and no significant increase over controls in combined benign and malignant liver tumors. It should also be noted that there was no increase in hepatocellular adenoma or carcinoma in the male mice dosed at 5 ppm. Male mice metabolically activate more CCl4 and experience a higher incidence of liver cancer than females. **PUBLIC COMMENTS: points against low-dose linear mechanism** EPA should prepare an independent, clear, and robust MOA analysis for both alternatives. EPA is obligated, under the statute, regulation, and Agency-wide guidance, to calculate potential risks from the alternative MOA, and the default option, and to characterize each fully, both narratively and quantitatively, for the risk manager. EPA should utilize an established framework to organize evidence for MOA based on side-by-side WOE	tumors by carbon tetrachloride have been extensively investigated. Metabolism is identified as the first key event for the induction of liver, adrenal tumors and brain tumors by carbon tetrachloride. The other key events by which carbon tetrachloride induces pheochromocytomas in mice and neuroblastomas and brain tumors in humans are currently unknown due to lack of mechanistic information on these tumor types. Biological support exists for a hypothetical MOA involving metabolism of carbon tetrachloride by CYP2E1, sustained cytotoxicity, and regenerative cell proliferation as key events driving the steep nonlinear increase in liver tumor dose-response at relatively high carbon tetrachloride exposures. However, several pieces of evidence suggest that carbon tetrachloride carcinogenicity is not explained by a cytotoxic-proliferative MOA in tumor types other than liver. At lower exposure levels, the correspondence between hepatocellular cytotoxicity and regenerative hyperplasia and the induction of liver tumors is inconsistent. In particular, liver findings from the JBRC bioassay (Nagano et al., 2007) suggest that mouse hepatocarcinogenicity cannot be explained in terms of the cytotoxic-proliferative MOA. An increased incidence of hepatocellular adenomas occurred in the low-exposure (0.9-ppm adjusted) female mouse in the absence of nonneoplastic liver toxicity, raising the possibility of another MOA operating in addition to or in conjunction with the cytotoxic-proliferative MOA. Other considerations suggest that the carbon tetrachloride database is insufficient to rule out other MOAs at low exposure levels, in particular considerations related to the compound's genotoxicity and general reactivity.

	comparison of alternative plausible MOAs (*e.g.*, AOPs, IPCS, Becker et al., 2017). A systematic and explicit approach must be uniformly implemented to compare potentially relevant MOAs. One method for doing this involves deriving WOE confidence scores based on the IPCS framework and Bradford Hill causation criteria. Significant effort has been directed to characterizing the MOA/AOPs at these sites, with agreement on this point not yet realized. Some additional work is needed, which will also lead to consensus on the appropriate choice(s) for dose response assessment. At present, the MOA analysis in the draft risk evaluation summarizes EPA's prior IRIS analysis with no updates or use of WOE analysis methods. Further, the IRIS analysis was published 10 years ago; thus, EPA should examine whether those conclusions still reflect the current state of the science. The SACC should discuss and advise EPA on providing a more thorough discussion surrounding the uncertainty for each alternative and on whether EPA should also include a determination of confidence in the selection of a particular MOA. EPA's position in the risk evaluation of a low-dose linear MOA for liver tumors is untenable in light of the most-up-to-date scientific studies on CCl4 toxicity. Uehara et al. (2013) showed that there was no secondary DNA damage associated with CCl4 radical-induced lipid peroxidation and/or cytotoxicity at the time points measured at a relatively low dose of CCl4 that also resulted in liver tumors in mice. This lack of concordance between DNA	Therefore, EPA considers alternate MOAs such as (1) cytotoxic mechanisms at high doses with alternate, non-cytotoxic mechanisms as lower doses, and (2) cytotoxicity and regenerative hyperplasia for liver tumors, in conjunction with the lack of MOA information on other tumor types induced by carbon tetrachloride in the animal and human data. The alternate MOAs and uncertainties in the cancer MOA for the different tumor types are addressed in the final risk evaluation by cancer dose response analysis and cancer risk calculations based on both linear and nonlinear approaches which encompass all the considered MOAs.

	adducts and cellular oxidative stress in liver tumor-bearing mice dosed with CCl4 provides critical evidence supporting a cytotoxic-proliferative (non-linear) MOA for CCl4 carcinogenicity at low doses. In describing the cytotoxic MOA in Table 3-11, EPA should consider whether the results in female mice are consistent with other animal studies and describe other data that substantiate the counterfactual argument against this MOA. Given the uncertainties in the current draft MOA analysis, EPA needs to revisit this entire section and provide a more comprehensive evaluation using, for example, the evolved qualitative MOA framework of WHO/IPCS or the quantitative MOA confidence scoring method described in Becker et al. (2017). Based on a considerable number of scientific studies, the MOA can be explained by the involvement of cytotoxicity and proliferation from the highly reactive radical metabolites of CCl4. The best available science and the weight of the scientific evidence indicate that CCl4 is carcinogenic in the liver only via a MOA with a non-linear (threshold) dose-response. **PUBLIC COMMENTS: points for low-dose linear mechanism** EPA's final evaluation should continue to conclude that evidence for a non-linear MOA is inadequate.	
SACC, 31, 39, 43, 45	**SACC COMMENTS: low dose risk calculation** The draft risk evaluation appears to present two approaches to calculating low-dose risk (a low dose linear approach and a non-linear approach), these two approaches appeared to be melded into a single risk assessment model	The final risk evaluation presents a low dose linear extrapolation and threshold risk assessment approaches. The evidence on cancer MOA has been revisited and expanded for liver, adrenal and brain tumors. In addition, the key events for the liver tumors MOA and uncertainties of alternate MOAs

	(lines 621 and 4325). The low dose linear approach was used for "low dose exposures of carbon tetrachloride." The nonlinear approach was used only for doses "exceeding the POD" of 18 mg/m^3. • It was not clear to the Committee how the non-linear approach is to be implemented. Both the linear and non-linear approaches are alternative approaches for quantifying *low dose* risk. • The Committee does not understand what it meant for the non-linear approach to be implemented for high doses only. • Some members noted that this confusion was due to the draft risk evaluation's reliance on IRIS (U.S. EPA, 2010) for its human health risk evaluations. Given this, the Committee wondered whether any discussion of cancer induction mechanism was needed in the risk evaluation, since, again, none of it seems to be used for purposes of either qualitative or quantitative human health risk evaluation. • Some Committee members agreed with EPA's determination while other disagreed based on the MOA for this chemical and its free radical metabolites. Some Committee members would like to see a nonlinear threshold-type of approach also presented for the cancer risks based on long-standing, published, peer-reviewed evidence regarding the peroxyl radical-based mechanisms by which CCl4 induces tumors. Recommendation: State clearly and justify whether a low-dose linear risk assessment approach or a non-linear risk assessment approach is preferred. • The Committee concluded that the weight of a considerable body of scientific evidence indicates that the relationship between CCl4 dose/exposure and its	are presented in appendices of the final risk evaluation. (U.S. EPA, 2010) concludes that the key events in the cancer MOA for liver tumors described in section **Error! Reference source not found.** of the final risk evaluation appear to play a significant role at high exposure doses. Therefore, EPA considers an alternate MOA that combines cytotoxic mechanisms at high doses with alternate, non-cytotoxic mechanisms as lower doses. Metabolism is identified as the first key event for the induction of liver, adrenal tumors and brain tumors by carbon tetrachloride. The other key events by which carbon tetrachloride induces pheochromocytomas in mice and neuroblastomas and brain tumors in humans are currently unknown due to lack of mechanistic information on these tumor types. There is general consensus that metabolism of carbon tetrachloride leads to the production of free peroxy radicals which induce oxidative stress that can damage proteins, DNA and lipids. As described in the IRIS assessment, *in vitro* studies by (Colby et al., 1994) showed that preincubation of adrenal microsomes with 1-aminobenzotriazole, a CYP450 suicide inhibitor, prevented the effects of carbon tetrachloride on lipid peroxidation and covalent binding. Nevertheless, there is not sufficient information to elucidate the key events for cancer induction in the adrenal gland and brain tissues. One of the general considerations for MOA analysis in the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005) for analyzing an agent's influence in the development of tumors is the consideration of an agent working by more than

	genotoxic response is nonlinear with a steep dose-response. • The Committee noted that pheochromocytomas are tumors of chromaffin cells in the adrenal gland. CCl4 is among the small number of chemicals that can cause adrenal tumors in mice, and also cause liver tumors. • The Committee briefly discusses available data relevant to CCl4 and adrenal tumors, concluding that genotoxic events in the adrenal appear to be attributable to the indirect action of free radicals. • If one assumes that the key steps are the same in adrenal gland and liver tumors, extrapolation using a non-linear, threshold model would seem appropriate. This would also be supported by the *in vitro* and the systemic *in vivo* genotoxicity data for CCl4, which are generally negative. • One Committee member suggested that CCl4, like other carcinogens, with multiple interacting MOAs will operate as additive to background. As a result, the dose-response relationship may look quite linear, especially in a heterogenous population of humans (Crump, 2018). • Several points supporting the SACC conclusion are provided in the report. The Agency needs to be clear about what the terms "linear low-dose" or a non-linear or threshold dose-response means. • Rather than separately defining low-dose sub-linear and threshold, EPA (2005) defines "low-dose nonlinear" as a dose-response "whose slope is zero at a dose of zero." Note that this includes both low-dose sub-linear and threshold dose-responses as defined by	one MOA at different sites and at the same tumor site. Therefore, the cancer MOA cannot be generalized to other tissues or cell types without additional analyses. Based on the reasonably available information and cancer MOA considerations in (U.S. EPA, 2005), EPA concludes that all the key events in the MOA for carbon tetrachloride carcinogenicity in adrenal gland and brain tissues across all exposure levels is unknown at this time. Therefore, EPA considers alternate MOAs such as (1) cytotoxic mechanisms at high doses with alternate, non-cytotoxic mechanisms as lower doses, and (2) cytotoxicity and regenerative hyperplasia for liver tumors, in conjunction with the lack of MOA information on other tumor types induced by carbon tetrachloride in the animal and human data. The alternate MOAs and uncertainties in the cancer MOA for the different tumor types are addressed in the final risk evaluation by cancer dose response analysis and cancer risk calculations based on both linear and nonlinear approaches which encompass all the considered MOAs.

	Crump (2011) and the EPA cancer guidelines (U.S. EPA 2005) but does not include supra-linear dose-responses. • The EPA guidelines do not discuss or define supra-linearity. • In order to conclude that the low dose-response is non-linear or threshold, it is not sufficient to conclude that carcinogenicity is not produced via a mutagenic MOA. There are mechanisms other than mutagenicity that can produce a low-dose linear response. Recommendation: EPA should apply a non-linear model in estimating cancer risks, in light of the preponderance of evidence that lipid peroxidation- and endonuclease-derived mutations, and other cytotoxic effects, are the origins of tumors of the liver and adrenal gland. Recommendation: Consider adopting a threshold-type MOA in estimating carcinogenic risk and consider applying UFs for database deficiencies due to more limited mechanistic information about adrenal gland tumors in mice and reported associations of occupational CCl4 exposure and increased incidence of gliomas in workers. Public commenters suggested, and the Committee agreed, that when there was conflicting information on the cancer MOA, EPA should, at a minimum, include a risk characterization for both linear and non-linear dose-response models to allow for comparison of the results. The SACC suggested selecting the most conservative model for the evaluation of risks. **PUBLIC COMMENTS: low dose risk calculation** Given the strong evidence supporting the hypothesized	

	alternative approach (threshold cytotoxicity MOA), and the uncertainties in the MOA that EPA has postulated invokes the no-threshold, low-dose linearity default, EPA must quantify risks for both approaches fully. In its TSCA risk evaluations, EPA should more clearly and transparently present biologically robust, MOA assessments where the WOE is integrated fully. Ultimately, EPA should carry any biologically plausible alternative MOAs and the default MOA option through the entire assessment and present all risk calculations in the risk characterization section. To do otherwise is inconsistent with the TSCA statute, the TSCA Risk Evaluation Rule, and the Agency's Cancer Guidelines. In the 2010 CCl4 IRIS assessment, EPA concluded that there is insufficient information on the MOA of CCl4 for mouse liver tumors at low doses and the mouse pheochromocytomas to support a non-linear dose-response approach for assessing cancer risk. In spite of that conclusion, a majority (four out of six) of the EPA Science Advisory Committee review for the 2010 CCl4 IRIS assessment recommended that the CCl4 cancer risk should be preferably based on a non-linear threshold method. EPA did not refer to the impact on the risk estimate of the policy chosen dose-response model, the linearized multistage model (LMS). Alternative models would give risk values several orders of magnitude lower than the LMS model. EPA should provide added justification for moving forward with quantification of risk associated with only one of the MOAs. Additionally, the SACC should discuss	

	and evaluate whether EPA should quantify risks for both alternatives, or at a minimum, include a sensitivity analysis to examine whether the MOA analysis influences the risk conclusions.	
45	**PUBLIC COMMENTS:** The draft risk evaluation describes the two quantitative approaches for assessment of carcinogenicity in the IRIS Toxicological Review (U.S. EPA, 2010), but states in number 2 on p. 135, "This threshold approach is used in this risk evaluation for high exposures based on a benchmark MOE of 30." However, in the risk evaluation, the threshold approach is not described further and does not appear to be used in this manner.	The statements on threshold approach were corrected or eliminated in the final risk evaluation.
SACC	**SACC COMMENTS:** • There appeared to be no description of the calculation of the POD of 18 mg/m^3 in the document. Recommendation: Explain the basis and the calculations in determining the PODs.	The basis and calculations in determining the PODs have been incorporated in the final risk evaluation.
SACC, 29	**SACC COMMENTS: IUR calculation** Recommendation: Key details on the derivation of the IUR, similar to that provided in the IRIS summary (*i.e.*, species, cancer type, extrapolation model, risk levels, etc.), should also be provided in this risk evaluation. **PUBLIC COMMENTS:** As pheochromocytomas occurred in mice at exposure concentrations that also resulted in toxicity in liver cells, estimation of human cancer risk based on liver toxicity would be adequately protective for both tumor types.	Key details on IUR derivation have been added to section 3.2.5.2.5. IUR estimates based on the tumor data sets in (Nagano et al., 2007) were calculated using the following equation: IUR = BMR ÷ HEC, where BMR = benchmark response, HEC = human equivalent concentration. The highest estimated IUR for carbon tetrachloride via the inhalation pathway is 6×10^{-6} ($\mu g/m^3$)$^-$1, which is associated with pheochromocytomas in the male mouse. The data set on pheochromocytomas in the male mouse was determined to be applicable, scientifically sound, and yielded the highest estimate of risk and is supported by the EPA IRIS Program (U.S. EPA, 2005).
30	**PUBLIC COMMENTS:**	Temporal adjustments were performed using experimental data and/or PBPK modeling described in sections 3.2.5.2.1.

	Studies are needed that would illuminate the potential for general systemic toxicity over exposure duration(s) commensurate with that/those of the actual exposure scenario(s) under evaluation or, if long term, that could be extrapolated from shorter-term exposure studies accompanied by the application of a UF representing that extrapolation (*e.g.*, acute short term or subchronic to chronic).	and 3.5.2.5.2.2, therefore EPA didn't apply UFs when extrapolating for exposure time duration.
43	**PUBLIC COMMENTS:** The 2010 IRIS assessment and the 2014 NATA show that the risk to most Americans from ambient air exposure to CCl4 exceeds the 1-in-a-million lifetime risk level. Yet EPA's risk evaluation ignores this evidence of excess cancer risk to the general population, as well as to particularly exposed subpopulations, based on its exclusion of all air emissions from the evaluation's scope. EPA also fails to consider the impacts of these background CCl4 concentrations on the workers and ONUs studied in the risk evaluation who are exposed in the workplace, and thus understates the risks to this population from aggregate exposure to CCl4.	EPA did not consider background exposure that workers might be exposed to in addition to exposures from TSCA-conditions of use. This may result in an underestimation of risk, and additional discussion of this underestimation has been added to the document in the Assumptions and Key Sources of Uncertainty section. EPA relied on NIOSH guidance in order to establish 10^{-4} as the cancer risk benchmark for workers, although acknowledging that other laws have standards that differ from TSCA's. In addition to assessing the cancer risk using a linear extrapolation approach and comparing the results to the standard cancer benchmark of $1x10^{-4}$, EPA also assessed cancer risk using a threshold approach. Based on the threshold approach, EPA identified MOEs for cancer risks. EPA used both the risk estimates derived from the linear extrapolation approach and the MOEs derived from the threshold approach for the unreasonable risk determinations for individuals exposed to carbon tetrachloride. TSCA section 6(b)(4)(F)(ii) directs EPA to "describe whether aggregate or sentinel exposures to a chemical substance under the conditions of use were considered, and the basis for that consideration" in risk evaluations. EPA defines aggregate exposures as the combined exposures to an

		individual from a single chemical substance across multiple routes (*i.e.*, dermal, inhalation, or oral) and across multiple pathways (*i.e.*, exposure from different sources). 40 CFR 702.33. EPA defines sentinel exposures as the exposure from a single chemical substance that represents the plausible upper bound of exposure relative to all other exposures within a broad category of similar or related exposures. 40 CFR 702.33. EPA considered the reasonably available information and used the best available science to determine whether to consider aggregate or sentinel exposures for a particular chemical. EPA has determined that using the high-end risk estimate for inhalation and dermal risks separately as the basis for the unreasonable risk determination is a best available science approach. There is low confidence in the result of aggregating the dermal and inhalation risks for this chemical if EPA uses an additive approach, due to the uncertainty in the data. EPA does not have data that could be reliably modeled into the aggregate, which would be a more accurate approach than adding, such as through a PBPK model. Using an additive approach to aggregate risk in this case would result in an overestimate of risk. Given all the limitations that exist with the data, EPA's approach is the best available science. EPA has added language to the Key Assumptions and Uncertainties section describing these assumptions and uncertainties.
39	**PUBLIC COMMENTS:** The repetition of the 2010 CCl4 IRIS assessment for the risk evaluation does not fulfill the requirements of the Lautenberg Act with the use of the best available science and decisions based on the weight of the scientific evidence.	EPA has used information consistent with the best available science, as required by TSCA Section 26(h). EPA comprehensively reviewed key studies from the 2010 IRIS assessment in addition to epidemiological and animal studies as well as invitro information published after publication of the 2010 IRIS assessment.

39	**PUBLIC COMMENTS:** The draft risk evaluation continues to rely on the same methodology that EPA has followed for 40 years, as evidenced inter alia by its references to the 2005 Guidelines for Carcinogen Risk Assessment and the 2010 IRIS review of CCl4. The methodology incorporated generic policy choice default assumptions that date from the 1970s. The criteria for data interpretation and analysis are policy choices resulting in the regulatory use of an upper confidence limit value calculated using only a selected part of the data. This is not in accordance with TSCA § 26(h) and (i).	When synthesizing and integrating evidence for each human health hazard endpoint, EPA considered quality, consistency, relevancy, coherence and biological plausibility as specified in *Application of Systematic Review in TSCA Risk Evaluations*. Sections 3.2.1 and 3.2.4 describe EPA's process of weighing and integrating scientific evidence for hazard endpoints. EPA is developing and implementing more formal and structured data integration strategies for the next set of TSCA chemical risk evaluations. In addition, EPA anticipates feedback from the NASEM TSCA Committee on its systematic review process and will carefully review and implement relevant recommendations.
43	**PUBLIC COMMENTS:** EPA's risk evaluation should account for acute cancer risks to workers and consumers. There exists a recognized methodology for extrapolating from findings of carcinogenicity in long-term studies to exposures of short duration (NRC, 2011). Rather than summarily dismissing acute cancer risks as impossible to estimate, EPA should have quantified these risks using the framework outlined by the National Research Council (NRC).	EPA relies on current agency guidance and risk assessment practice for developing cancer assessments in TSCA risk evaluations.
Methods used for dermal exposures		
SACC, 39, 43, 45	**SACC COMMENTS:** • The calculation of the dermal slope factor on pp. 134-135 of the draft risk evaluation is incorrect. To estimate a slope factor based on absorbed rather than gross dose, correction for an assumed pulmonary bioavailability of 63% is attempted. However, division by 63, rather than 0.63 results in a 100-fold underestimation of the dermal slope factor. Since carcinogenic risk is linearly related to carcinogenic potency, this means that all worker dermal pathway cancer risk evaluations are also underestimated by a factor of 100.	Calculations have been corrected in section 3.2.5.2.5 of the risk evaluation.

	• The SACC report highlights mistakes in the equation strings on lines 4334-4342 (pp. 134-135). • A member of the Committee warned that the primary conclusions of the draft risk evaluation were very sensitive to the error made in calculation of the dermal carcinogenic slope factor (DSF). The error (100X) was so large that no plausible adjustment to the assumed glove PFs could compensate for it. The final risk evaluation for CCl4 should find unreasonable risk for all worker conditions of use. Recommendation: Correct the calculation of the cancer slope factor for dermal exposure and adjust the risk calculations accordingly. **PUBLIC COMMENTS:** An error in calculating the cancer slope factor for dermal exposure resulted in underestimating cancer risk from the route by two orders of magnitude. EPA uses Equation 3-2 (p. 134 of the draft risk evaluation) to calculate a POD for chronic dermal exposures for a noncancer endpoint. In this equation, the dermal absorption factor is eliminated because an external inhalation exposure concentration is extrapolated to a dermal retained dose. Based on the information provided in the risk evaluation, the HED_{dermal} is 31.1 mg/m^3 x 1.25 m^3/hour x 8 hours/day x 0.63 retained inhaled dose fraction / 80 kg = 2.45 mg/kg-day. EPA seems to have used the percent value (63%) rather than the fraction (0.63), resulting in the HED_{dermal} being 100-fold greater or 245 mg/kg-day. Correcting this error will cause the estimated cancer risk to	

	increase significantly and impact EPA's determinations of unreasonable risk for workers and other subpopulations. The adjustment for inhalation absorption should be 1/0.63, not 1/63. Thus, the correct dermal cancer slope factor (CSF) is $8x10^{-2}$ per mg/kg-day. For the cancer risk estimate, the corrected dermal slope factor is $8x10^{-2}$ per mg/kg-day as retained dose. Based on the estimated dermal chronic retained dose for cancer of 0.1 mg/kg-day for central tendency and 0.39 mg/kg-day high end, the corresponding risk estimates are $8x10^{-3}$ and $3x10^{-2}$, respectively. Thus, as with the chronic noncancer endpoint, appropriate glove use in a production facility with a PF of 20 would result in cancer risk close to $1x10^{-4}$ for the central tendency and slightly above for the high-end dermal exposures. It is unclear why EPA referred to a value of 0.8% to adjust the IUR for dermal absorption (see p. 149). The dermal CSF calculated in the risk evaluation is based on the retained dose from inhalation exposure and is used to calculate risk from retained dose from dermal exposure assuming 4% absorption. Use of 0.8% dermal absorption rather than the 4% value results in an additional 5-fold reduction in risk.	
SACC, 39	**SACC COMMENTS:** • The Jongeneel study was presented as a Rijksinstituut voor Volksgezondheid en Milieu (RIVM) letter report to the National Institute for Public Health, which may mean that it is considered gray literature rather than peer reviewed. It was not referenced in PubMed, making it difficult to determine if it is routinely referenced as an appropriate approach.	This equation is similar to equations used by other First-10 chemicals (*i.e.*, methylene chloride) risk evaluations. Nonetheless, the equation was replaced with a peer-reviewed equation used in previous TSCA risk evaluations.

	Recommendation: Provide justification for the use of the Jongeneel equation to extrapolate chronic inhalation HEC to chronic dermal HED.	
SACC	**SACC COMMENTS:** Regarding the POD for occluded conditions: • Using liver toxicity data from a single animal in an unacceptable study to determine the NOAEL seems questionable. One cannot assume that induction of liver toxicity is unlikely for animals dermally exposed for 4 hours to 0.5 ml CCl4 just because that toxicity was not observed at that time point in one animal. A 4-hour exposure could induce liver toxicity that did not manifest until a later time point. Thus, this cannot be used to obtain a NOAEL. Third, the NOAEL seems to be calculated under the assumption that the animals in the Kronevi (1979) study were exposed to 0.5 ml of CCl4, when they were in fact exposed to 1.0 ml. This indicates that a faulty NOAEL of 110 mg/kg/day, rather than 216 mg/kg/day, was used. • EPA noted that the POD of 2,750 mg/kg/day is similar to a POD of 2,450 mg/kg/day derived by using the chronic inhalation values to extrapolate a chronic dermal value, and then further extrapolating an acute dermal POD by inexplicably multiplying by a factor of 10. Just because two questionable methods end up with similar values did not seem to be sufficient justification for their use. Recommendations: (1) Explain why a poor-quality study (Kronevi, 1979) was used to establish the acute dermal POD when so many other better quality studies were dismissed; (2) acknowledge that there are insufficient data to devise an acute dermal NOAEL and POD using the Kronevi (1979) study; (3) use the LOAEL from the	Non cancer dermal POD is now extrapolated from inhalation information due to dermal data limitations.

	Wahlberg and Boman (1979) study to determine the POD for acute occluded dermal exposure to CCl4; and (4) use the POD for occluded dermal exposure derived from the Wahlberg and Boman (1979) LOAEL to calculate a POD for acute non-occluded dermal exposure.	
30	**PUBLIC COMMENTS:** EPA explicitly asserts that the inhalation assessment is protective of heavy alcohol users and is silent on that point with regard to the dermal assessment, although one might interpret equivalency.	Information on Intraspecies UF has been updated based on SACC recommendations, which are applicable to both inhalation and dermal exposures (See section 3.2.5.2 of the risk evaluation).

Risk Characterization
Charge Question 5.1: Please comment on whether the information presented supports the finding outlined in the draft risk characterization section. If not, please suggest alternative approaches or information that could be used to further develop risk estimates within the context of the requirements stated in EPA's Final Rule, Procedures for Chemical Risk Evaluation Under the Amended TSCA (82 FR 33726). **Charge Question 5.2:** Please comment on the characterization of uncertainties and assumptions including whether EPA has presented a clear explanation of underlying assumptions, and accurate contextualization of uncertainties. Please provide information on additional uncertainties and assumptions that EPA has not adequately presented. **Charge Question 5.3:** Please comment on the validity of specific confidence summaries presented in section 4.5. **Charge Question 5.4:** Please comment on the objectivity of the selection of the data used to support the risk characterization and the sensitivity of the agency's conclusions to analytic assumptions made. **Charge Question 5.5:** Please comment on any other aspects of the human health risk characterization that has not been mentioned above. **Charge Question 5.6:** Please comment on whether the risk evaluation has adequately addressed potentially exposed or susceptible subpopulations in Sections 3.2.5.4 and 4.3. **Charge Question 5.7:** Please comment on whether the risk evaluation document has adequately described the uncertainties and data limitations associated with the methodologies used to assess the human health risks with respect to potentially exposed or susceptible subpopulations. Please comment on whether this information is presented in a clear and transparent manner. **Charge Question 5.8:** Please comment on whether EPA has adequately, clearly, and appropriately presented the reasoning, approach, assumptions, and uncertainties for characterizing risk to workers using PPE.

#	Summary of Comments for Specific Issues Related to Charge Question 5	EPA/OPPT Response
Overall risk approach		
SACC, 26, 38, 43	**SACC COMMENTS: cancer benchmark** • A Committee member found the discussion in Section 5.1.2.2, Determining Cancer Risks (p. 173), to be unclear and disagreed with the choice of 10^{-4} as an acceptable risk. • EPA should also consider the approach described in Chiu and Crump (2012) in the derivation of unit risk. **PUBLIC COMMENTS: cancer benchmark** EPA cites a NIOSH guidance document that recommends the use of a 1 in 10,000 cancer threshold when determining risk management limits (RMLs) for carcinogens. NIOSH, however, is not required to set RMLs at levels that avoid unreasonable risk to potentially exposed and susceptible subpopulations. Moreover, as NIOSH has explained, "[a]n excess lifetime risk level of 1 in 10,000 is considered to be a starting point for continually reducing exposures in order to reduce the remaining risk … [F]or most carcinogens, there is no known safe level of exposure … [and] NIOSH will continue to recommend that employers reduce worker exposure to occupational carcinogens as much as possible through the hierarchy of controls, most importantly elimination or substitution of other chemicals that are known to be less hazardous…" EPA's use of a 1 in 10,000 cancer risk level as reasonable for workers is deeply flawed. EPA's decision is wholly at odds with its own acknowledgment that other laws have standards that differ from TSCA's (p. 172, footnote 21).	As noted in the draft risk evaluation, EPA relied on Agency precedent and NIOSH guidance when choosing the 10^{-4} cancer risk benchmark to evaluate risks to workers from carbon tetrachloride exposure. NIOSH's mandate, on pg. iii of (Whittaker et al., 2016), is to: "… describe exposure levels that are safe for various periods of employment, including but not limited to exposure levels at which no employee will suffer impaired health or functional capacities or diminished life expectancy as a result of his work experience." Although NIOSH guidance, p. 20, states that: "exposures should be kept *below* a risk level of 1 in 10,000, *if practical* [emphasis added]" EPA adheres to the 1 in 10,000 benchmark during the risk evaluation stage for TSCA chemicals. The standard cancer benchmarks used by EPA and other regulatory agencies range from 1 in 1,000,000 to 1 in 10,000 (*i.e.*, $1x10^{-6}$ to $1x10^{-4}$) depending on the subpopulation exposed. EPA has consistently applied a cancer risk benchmark of $1x10^{-4}$ for assessment of occupational scenarios under TSCA. This is in contrast with cancer risk assessments for consumers or the general population, for which $1x10^{-6}$ is applied as a benchmark. EPA, consistent with 2017 NIOSH guidance, used $1x10^{-4}$ as the benchmark for the purposes of unreasonable risk determinations for individuals exposed to carbon tetrachloride in industrial and commercial work environments, including workers and ONUs. $1x10^{-4}$ is not a bright line and EPA has discretion to make unreasonable risk determinations based on other benchmarks as appropriate.

	EPA is required to protect workers, both generally and as a "potentially exposed or susceptible subpopulation," under TSCA, not under OSHA. The 2016 amendments to TSCA strengthened EPA's already-existing mandate to protect workers. TSCA's new definition of "potentially exposed or susceptible subpopulation" has no asterisk next to workers, and there is no basis in TSCA for EPA to provide less protection to workers than any other such subpopulation, let alone than the general population. Yet that is exactly what EPA has done here. The 2016 amendments to TSCA also explicitly preclude EPA from considering feasibility or other non-risk factors when determining whether a chemical presents an "unreasonable risk," including to workers. EPA cannot point to any legislative history suggesting that TSCA adopted OSHA's standard. Moreover, if Congress had intended to adopt the Benzene standard under TSCA, it would have required that EPA regulate "significant risks," not "unreasonable risks." Indeed, the significant differences between the language and structure of the two statutes strongly indicates that Congress meant to adopt a different standard in TSCA, not the standard articulated by the Court in the Benzene case. When Congress amended TSCA to include the unreasonable risk standard, it did so knowing that agency practice was to regulate cancer risks at the 10^{-6} risk level. It should be presumed that Congress meant to adopt this risk standard when codifying the unreasonable risk standard. EPA blurs a critical distinction made when EPA has invoked the less stringent level of protection from cancer risks: the level set to reflect the maximum risk faced by	See section 5.1.1.2 of the risk evaluation for additional information. In addition to assessing the cancer risk using a linear extrapolation approach and comparing the results to the standard cancer benchmark of $1x10^{-4}$, EPA also assessed cancer risk using a threshold approach. Based on the threshold approach, EPA identified MOEs for cancer risks. EPA used both the risk estimates derived from the linear extrapolation approach and the MOEs derived from the threshold approach for the unreasonable risk determinations for individuals exposed to carbon tetrachloride. In consideration of the uncertainties and variabilities in PPE usage, EPA uses the high-end exposure value when making its unreasonable risk determination in order to address those uncertainties.

	any individual versus the level set to protect a broader population. EPA invokes the "two-step approach" used under the CAA and the two-step, risk-based decision framework for the National Emission Standard for Hazardous Air Pollutants (NESHAP). But in this risk evaluation, EPA has set a risk level for the entire worker population that is the same as the level that EPA elsewhere set for the most exposed individual in a population. EPA then erroneously invokes this level repeatedly to find a number of conditions of use of CCl4 to pose no risk to any workers, thereby subjecting many tens of thousands of workers to cancer risks that are as much as two orders of magnitude higher than warranted. This approach must be rejected on scientific as well as legal grounds. EPA should use a benchmark of $1x10^{-6}$ to determine whether cancer risks to workers and consumers are unreasonable under TSCA. The SACC has previously stated that EPA has not provided "adequate explanation and justification" for this reduced threshold and the CCl4 draft evaluation also fails to justify EPA's approach. EPA's recent draft risk evaluations maintains that risks $<1x10^{-4}$ will be considered "reasonable" under TSCA because, "consistent with case law and 2017 NIOSH guidance," this risk level applies to "industrial and commercial work environments subject to OSHA requirements." EPA fails to explain why OSHA precedent should control decision-making under TSCA. For all occupational conditions of use, EPA calculates increased cancer risks from CCl4 between 1 in 10,000 and 1 in 1,000,000, even after assuming the use of respirators and other PPE. Had EPA applied its standard 1 in	

	1,000,000 unreasonable risk threshold, all of those occupational risks would have been classified as unreasonable and regulated under TSCA. However, because EPA used a less protective risk threshold for workers, no workers who manufacture or directly use CCl4 will be protected.	
SACC, 23, 26, 30, 32, 38, 42, 43	**SACC COMMENTS: aggregate exposure** Recommendation: Consider assessing combined dermal and inhalation exposure for workers since it is very unlikely that dermal exposure to CCl4 would occur in the absence of inhalation exposure. **PUBLIC COMMENTS: aggregate exposure** Of greatest concern is EPA's failure to aggregate dermal and inhalation exposure and derive composite risk estimates even though the draft risk evaluation indicates that "inhalation and dermal exposures are assumed to occur simultaneously for workers." EPA acknowledges that its "glove protection factors are based on . . . 'what-if' assumptions and are highly uncertain" and that it "does not know the actual frequency, type, and effectiveness of glove use in specific workplaces of the occupational exposure scenarios." Given these admissions, it is hard to understand how EPA can dismiss aggregate inhalation and dermal exposure as "highly unlikely." EPA should: (1) model a broader range of dermal contact scenarios based on its own analysis of variations in dermal exposure conditions; and (2) aggregate dermal and inhalation exposures since these two routes of exposure occur simultaneously and EPA has no plausible basis to conclude that use of gloves will prevent dermal contact with CCl4.	TSCA section 6(b)(4)(F)(ii) directs EPA to "describe whether aggregate or sentinel exposures to a chemical substance under the conditions of use were considered, and the basis for that consideration" in risk evaluations. EPA defines aggregate exposures as the combined exposures to an individual from a single chemical substance across multiple routes (*i.e.*, dermal, inhalation, or oral) and across multiple pathways (*i.e.*, exposure from different sources). 40 CFR 702.33. EPA defines sentinel exposures as the exposure from a single chemical substance that represents the plausible upper bound of exposure relative to all other exposures within a broad category of similar or related exposures. 40 CFR 702.33. EPA has determined that using the high-end risk estimate for inhalation and dermal risks separately as the basis for the unreasonable risk determination is a best available science approach. There is low confidence in the result of aggregating the dermal and inhalation risks for this chemical if EPA uses an additive approach, due to the uncertainty in the data. EPA does not have data that could be reliably modeled for the aggregate exposure, which would be a more accurate approach than adding, such as through a PBPK model. Using an additive approach to aggregate risk in this case could result in an overestimate of risk. Given all the limitations that exist with the data, EPA's approach is the best available science. EPA has added language to the Key

	EPA claims that it "chose not to employ additivity of exposure pathways … because of the uncertainties present in the current exposure estimation procedures that may lead to an underestimate of aggregate exposure." Even if combining exposure routes "may lead to an underestimate of aggregate exposure," the failure to combine routes is known to lead to an even greater underestimate, since it unrealistically assumes that no worker will have both dermal and inhalation exposures. There is no basis for EPA to rely on false exposure assumptions or to ignore known combinations of inhalation and dermal exposures just because the calculation of more accurate, combined exposures presents "uncertainties." The lack of aggregation leads to an underestimate of exposure and risk and, potentially, an incorrect declaration of "no unreasonable risk" when one actually exists. assessments. Aggregation can be done relatively easily for the chronic exposure scenarios. The same study and set of endpoints are used for both the inhalation and dermal assessments, as the latter is extrapolated from the same data used for the inhalation assessment. This is true for both the noncancer (endpoint = fatty liver) and cancer (endpoint = increased tumor incidences [liver and pheochromocytoma]) Some extra effort would be required to do an aggregate assessment in the case of the acute exposure scenarios, given that different studies and different endpoints (one study in humans – neurotoxicity, the other in guinea pigs – liver) were used to derive PODs for each acute route of exposure. In addition to doing the necessary math to convert the administered or internal dose for each route to	Assumptions and Uncertainties section describing these assumptions and uncertainties. EPA did not consider background exposure that workers using products containing carbon tetrachloride might be exposed to in addition to exposures from TSCA conditions of use. Risks from background concentrations to carbon tetrachloride are assessed under the EPA NATA. The 2014 NATA reports a national ambient carbon tetrachloride concentration of 0.53 µg/m^3 and 3 in a million cancer risk. https://www.epa.gov/national-air-toxics-assessment/2014-nata-assessment-results#pollutant. This may result in an underestimation of risk, and additional discussion of this underestimation has been added to the document in the Key Assumptions and Uncertainties section. Clarifying language on exposure pathways and risks under the jurisdiction of other EPA-administered statutes have been added to section 1.4.3 of the final risk evaluation document. The products available for purchase by consumers are not expected to contain measurable amounts of carbon tetrachloride because carbon tetrachloride is not used in the manufacturing of the actual products. Trace levels of carbon tetrachloride in the chlorinated substances used to manufacture the products are expected to volatilize during the product manufacturing process. Furthermore, background concentrations to carbon tetrachloride are assessed under the EPA NATA. Therefore, consumer conditions of use were removed from the risk evaluation in the exercise of EPA's discretionary scoping authority under TSCA sec. 6(b)(4)(D) and EPA did not evaluate hazards or exposures to consumers or bystanders to consumer use in this risk evaluation.

	the same metric, a decision would have to be made as to what the appropriate benchmark MOE would be. EPA fails to consider the impacts of background CCl4 concentrations on the workers and ONUs studied in the risk evaluation, and thus understates the risks to this population from aggregate exposure to CCl4. EPA lacks adequate occupational exposure data to support its findings of no unreasonable risk, and it fails to account for the background CCl4 concentrations that workers are exposed to outside the workplace. These errors and omissions understate CCl4's occupational risks, in violation of TSCA's express requirement to protect workers. EPA disregards environmental pathways of human exposure that raise serious health concerns and makes the mistaken assumption that consumers are not exposed to CCl4.	
SACC	**SACC COMMENTS: working lifetime** Recommendation: Use a 45-year working lifetime instead of a 40-year lifetime to align with the NIOSH policy. It would also be useful to calculate risk using ranges of work lifetimes.	The cancer assessment for carbon tetrachloride is based on general exposure frequency (*i.e.*, the amount of days per year for workers or ONUs exposed to carbon tetrachloride) of 250 days per year and the occupational exposure duration was 40 years over a 70-year lifespan. The risk evaluation states that it is recognized that these exposure assumptions are likely yielding conservative cancer risk estimates, but EPA does not have additional reasonably available information for further refinement.

26, 30, 39, 41, 43	**PUBLIC COMMENTS: risk evaluation does not fulfill statutory requirements**	EPA appreciates this feedback. Additional discussion of risk underestimation has been added to the document in the Assumptions and Key Sources of Uncertainty section.

	Regrettably, the draft risk evaluation does not fulfill the requirements of the Lautenberg Act. Its hazard assessment is not based on the best available science; its exposure assessment does not utilize all of the available occupational exposure information; and it does not reflect the current industrial hygiene practices in place at facilities where CCl4 is produced. To maintain the credibility of its regulatory efforts under TSCA, it is imperative that EPA build upon the available information to construct a more realistic risk assessment before proceeding with rulemaking. EDF's analyses identify and quantify several major ways in which EPA has underestimated occupational risks, including through: its unsupported assumptions regarding worker use of PPE for all conditions of use; its use of a cancer risk benchmark level for workers that fails to protect them as a vulnerable subpopulation as required by TSCA; its failure to consider combined exposures of workers from multiple sources; its failure to identify unreasonable risks for the most highly exposed, and hence most vulnerable, of workers; and its suggestion that it may dismiss the few unreasonable risk findings it made by invoking "uncertainty." EPA finds CCl4 presents risks of concern for some conditions of use, and particularly for ONUs. However, due to critical scientific flaws in EPA's risk assessment approaches that lead to underestimation of risk, the actual risks are of greater magnitude that stated by EPA and additional conditions of use present unreasonable risks. Piecemeal determinations that isolated conditions of use	Under TSCA § 6(b), EPA is required to conduct risk evaluations to determine whether a chemical substance presents unreasonable risk of injury to health or the environment, under the conditions of use, without consideration of costs or other non-risk factors, including an unreasonable risk to potentially exposed or susceptible subpopulations, identified as relevant to the risk evaluation. Per 40 CFR 702.47 "…EPA will determine whether the chemical substance presents an unreasonable risk of injury to health or the environment under each condition of use within the scope of the risk evaluation…". This approach in the implementing regulations for TSCA risk evaluations, is consistent with statutory text in TSCA section 6(b)(4)(D), which instructs EPA to conduct risk evaluations to determine whether a chemical substance presents unreasonable risk of injury to health or the environment "under the conditions of use." Per the statute (see TSCA section 6(b)(4)(A)) and the implementing regulations for risk evaluations (40 CFR part 702, subpart B), EPA must make the unreasonable risk determination at the time of the risk evaluation. Upon finding unreasonable risk, EPA will apply risk management actions to the extent necessary so that the chemical no longer presents such risk, in accordance with TSCA section 6(a). As required by TSCA § (6)(b), EPA established, by rule, a process to conduct these risk evaluations. TSCA § 26(h) and (i) require EPA, when conducting risk evaluations, to use scientific information, technical procedures, measures, methods, protocols, methodologies and models consistent

	of CCl4 pose "no unreasonable risk" violates TSCA's plain text. EPA must revise its risk evaluation for CCl4 to make a single risk determination for the chemical substance as a whole. Based on EPA's findings that some conditions of use present unreasonable risks to health, EPA must conclude under TSCA section 6(b)(4)(A) that CCl4 presents an unreasonable risk to human health. EPA should re-evaluate all conditions of use for both the worker and ONU populations, implementing modifications to the exposure assessments, PODs, and benchmark MOEs recommended above. It is expected that some number of scenarios would flip from a declaration of "no unreasonable risk" to one of "an indication of unreasonable risk," increasing the number of scenarios requiring risk mitigation.	with the best available science and to base its decisions on the weight of the scientific evidence. While the law does not specifically define this term "unreasonable risk", during the risk evaluation process EPA weighs a variety of factors including the effects of the chemical on humans or the environment, the population exposed (including any sensitive subpopulations), the severity of the hazard, and uncertainties. This approach is outlined in EPA's 2017 *Procedures for Chemical Risk Evaluation Under the Amended TSCA* rule (risk evaluation rule) preamble on how risk evaluations will be conducted. [82 FR 33726, at 33735 (July 20, 2017)] To meet these TSCA § 26 science standards, EPA used the TSCA systematic review process described in the *Application of Systematic Review in TSCA Risk Evaluations* document. EPA believes the risk evaluation for carbon tetrachloride meets all requirements for risk evaluations identified under TSCA and its implementing regulations. In making the risk determinations, EPA considers relevant risk-related factors, including, but not limited to: the effects of the chemical substance on health and human exposure to such substance under the conditions of use (including cancer and non-cancer risks); the effects of the chemical substance on the environment and environmental exposure under the conditions of use; the population exposed (including any potentially exposed or susceptible subpopulations (PESS)); the severity of hazard (including the nature of the hazard, the irreversibility of the hazard); and uncertainties. EPA considers the uncertainties associated with each condition of use, and how the uncertainties may result in a

		risk estimate that overestimates or underestimates the risk. Based on such analysis, EPA determines whether or not the identified risks are unreasonable. Such consideration carries extra importance when the risk estimates are close to the benchmarks for risks from acute and chronic non-cancer health effects and cancer. To determine whether or not a condition of use presents unreasonable risks, EPA incorporates assumptions based on information and judgment underlying the exposure scenarios. These assumptions, which include assumptions regarding PPE use, are described in the unreasonable risk determination for each condition of use, in section 5.2. It is important to note that the benchmarks for cancer and non-cancer risk estimates are not bright lines, and EPA has discretion to make unreasonable risk determinations based on other risk benchmarks or factors as appropriate. EPA is making its unreasonable risk determinations on the high-end exposure value for workers and consumers and either the high-end exposure value or central tendency for ONUs, depending on the data, and factoring in the uncertainties due to UF factors. Additionally, EPA makes an unreasonable risk determination and makes no determination on reasonable risk.
26	**PUBLIC COMMENTS:** EPA inappropriately fails to find unreasonable risk to workers despite exceedances of its benchmarks for high-end exposures. Among other concerns, EPA's approach is at odds with its obligation under TSCA to conduct risk evaluations that ensure protection of "potentially exposed or susceptible subpopulations," which TSCA explicitly defines as including workers. TSCA does not permit EPA	The use of the high-end exposure value when making the unreasonable risk determination for workers accounts for potentially exposed or susceptible subpopulations (PESS). EPA found that there is unreasonable risk to workers for dermal exposures. For inhalation exposures, based on the high-end exposure value, EPA found that there is no unreasonable risk to workers when assuming use of PPE.

	to protect against only the "average or typical exposure;" in fact, when it comes to workers and other "potentially exposed or susceptible subpopulations," EPA is required to protect all of them.	TSCA section 3(12) lists examples of "potentially exposed or susceptible subpopulations" but neither that provision nor TSCA section 6(b) specifies subpopulations that must be considered PESS in any given risk evaluation. EPA therefore has the discretion to identify PESS that are relevant to a risk evaluation.
26, 38	**PUBLIC COMMENTS:** Despite assuming that ONU exposures "are expected to be lower than … exposures for workers directly handling the chemical," EPA concludes the only ONUs, and not direct occupational users, face unreasonable risk from CCl4. EPA is clearly suggesting that it may deem these four-fold exceedances of its own too-lax cancer risk benchmark by central tendency exposures not to constitute unreasonable risk because of the uncertainty in its estimates. Set aside that this uncertainty is the result of EPA having made no effort to obtain any actual exposure data for ONUs. EPA's own analyses in these cases showed that CCl4 presents an unreasonable risk, but EPA indicates that it may dismiss this unreasonable risk by invoking uncertainty in the data. This approach is arbitrary and capricious because EPA refuses to accept the outcomes of its own analyses, and EPA's conclusions run contrary to the evidence before the Agency. Based on the analysis presented in the draft risk evaluation, EPA should affirm that an unreasonable risk is presented to ONUs by these conditions of use.	EPA considers ONUs to be a subset of workers for whom the potential inhalation exposures may differ based on proximity to the exposure source. EPA assumed an absence of PPE for ONUs, since ONUs do not directly handle the chemical and are instead doing other tasks in the vicinity of carbon tetrachloride use. EPA also assumed that, in most cases, ONU inhalation exposures are lower than inhalation exposures for workers directly handling the chemical substance. For dermal exposures, because ONUs are not dermally exposed to carbon tetrachloride, dermal risks to ONUs were not assessed. Based on comments received on the draft risk evaluation, EPA was able to evaluate ONU inhalation exposures separately from workers for several carbon tetrachloride conditions of use, including domestic manufacturing. Consistent with the way that unreasonable risk determinations are made for workers, for these conditions of use with ONU-specific exposure estimates, EPA uses the high-end exposure value when making its unreasonable risk determinations in order to capture exposures for PESS. For the rest of the conditions of use, the difference between ONU exposures and workers directly handling the chemical cannot be quantified. EPA assumed that, in most cases, ONU inhalation exposures are lower than inhalation exposures for

		workers directly handling the chemical substance. For inhalation exposures, to account for those instances where, based on EPA's analysis, the monitoring data or modeling data for worker and ONU inhalation exposure could not be distinguished, EPA considered the central tendency risk estimate when determining ONU risk. The final unreasonable risk determinations are based on the risk estimates in the final risk evaluation, which may differ from the risk estimates in the draft risk evaluation due to peer review by the SACC and public comments. In the final risk evaluation, EPA has determined that most of the conditions of use present unreasonable risks to ONUs.
33	**PUBLIC COMMENTS:** EPA should be encouraged to consider conducting a multi-site risk estimate that accounts for the risks to multiple sites. Multi-site additivity is used by EPA if the tumors are occurring in the same strain, sex, and study in animal laboratory studies; this should have been done for human epidemiologic data. The lessons from the IRIS chloroprene assessment can be applied to this CCl4 assessment: linear extrapolation; use of age-dependent AFs; and evaluation of multi-site cancer risks.	Human epidemiological data on carbon tetrachloride has been used in a qualitative manner due to data limitations outlined in the TSCA risk evaluation.
Characterization of uncertainty and assumptions		
SACC, 30, 32, 43	**SACC COMMENTS: Intraspecies UF** • The two UFs generally applied (UF_A = 3 and UF_H = 10) do not account for the 10% risk at the BMDL or the uncertainty as to whether the NOAEL was actually a no-effect level. Therefore, another factor is needed to reduce the risk to an acceptable threshold, if a threshold was being assumed. It could also be argued that a factor is needed to account for the seriousness of the health effect.	To clarify the basis for the UFs, the following language was added to section 3.2.5, Dose Response Assessment: "EPA applied a composite UF of 30 for the chronic inhalation benchmark MOE, based on the following considerations: 1) **Interspecies uncertainty/variability factor (UFA) of 3** to account for species differences in animal to human extrapolation. An interspecies

	• EPA should review the UFs used for setting the maximum workplace concentration or Occupation Exposure Limits for CCl4 in Germany, the MAK (2000), that is based on its potential to cause toxicity, including tumors, in humans. • Another Committee member noted that Table 1-3 (pp. 27-28) includes assessments done by other countries, including the Health Canada guidelines for drinking water. The German MAK assessment should be added to Table 1-3. In addition, the risk evaluation should include more details on how the completed assessments were used in this risk evaluation. A 12-fold intra-human variability was found in the quantities of hepatic microsomal CYP2E1 (Snawder and Lipscomb, 2000). For this reason, the Committee member questioned if the UF for intra-human variability should be greater than 10 and suggested that a factor of 12 be used. • Another Committee member commented that sensitivity to CCl4 toxicity is directly correlated to the levels of CYP2E1 present in the individual. Recommendations: (1) Describe what the two UFs (UF_A and UF_H) represent and give some basis for their values; and (2) review and discuss UFs used by other expert bodies for CCl4 and consider any changes needed for this risk evaluation; explain how assessments from other jurisdictions were, or were not, considered for this risk evaluation. • There is a need to expand and clarify the UF discussions in the risk evaluation. The draft risk evaluation lacks a separate section that discusses how UFs should be applied under TSCA. It is difficult to	uncertainty/variability factor of 3 (UFA) was applied for toxicodynamic differences between species. This UF is comprised of two separate areas of uncertainty to account for differences in the toxicokinetics and toxicodynamics of animals and humans. In this assessment, the toxicokinetic uncertainty was accounted for by the PBPK modeling. As the toxicokinetic differences are thus accounted for, only the toxicodynamic uncertainties in extrapolating from animals to humans remain, and an UFA of 3 is retained to account for this uncertainty. **2) Intraspecies uncertainty/variability factor (UFH) of 10** to account for variation in sensitivity within human populations. An intraspecies uncertainty/variability factor of 10 (UFH) was applied for toxicokinetics and toxicodynamic differences in the human population due to humans of varying gender, age, health status, or genetic makeup might vary in response to carbon tetrachloride, including reasonably available quantitative information on human variability in CYP2E1 enzyme in adults." The following footnote was added to Table 1-3 (Assessment History of Carbon Tetrachloride) "The information in this table is based on Table1-1 in the Problem Formulation document and is not meant to be inclusive for all assessments from other countries." The following language was added to the PESS section "Heterogeneity in the human population distribution of microsomal enzymes metabolizing carbon tetrachloride has influence in the susceptibility to this chemical because

	determine from reading the many sections that discuss UFs in the draft risk evaluation the extent to which all pertinent factors are used to inform UFs, and whether the UFs applied adequately account for the uncertainties in the data and the methods used to derive risk estimates. • One Committee member noted that the draft risk evaluation is inconsistent in discussing uncertainties and data limitations associated with methodology limitations, and in particular how this impacts the assessment of health risks for PESS. • Transparency would be increased by having separate paragraphs for each of the PESS categories; this is recommended for alcohol consumption and variability in CYP2E1 status. • The Committee suggests summarizing the pertinent information in terms of what is known about each specific susceptibility category and indicating how this information has been included in the risk characterization. Recommendation: Expand and clarify the UF discussions, especially regarding PESS. **PUBLIC COMMENTS: Intraspecies UF** The draft evaluation fails to apply UFs necessary to account for elevated risks to vulnerable subpopulations and gaps in the CCl4 database. The Agency should provide substantive documentation that the 10-fold intra-human UF was, in fact, sufficient to accommodate for the impact of heavy alcohol use – a not-	metabolism is a hypothesized key event in carbon tetrachloride toxicity. Reasonably available quantitative information on the variation in human hepatic levels of the main metabolic enzyme, CYP2E1, demonstrates considerable intrahuman variability. For example (Lipscomb et al., 1997) reported a sevenfold range in activity of CYP2E1 among hepatic microsomal samples from 23 subjects. Snawder and Lipscomb (Snawder and Lipscomb, 2000) demonstrated 12-fold differences in CYP2E1 protein content between the highest and lowest samples from 40 samples of microsomes from adult human liver organ donors. Consideration of this PESS quantitative information is incorporated in the UFs used in the risk characterization." Section 3.2.5.4 of the final risk evaluation states that the variability in the response to carbon tetrachloride in relation to alcohol consumption is emphasized by the fact that an estimated exposure at 63 ppm-h was fatal in a heavy drinker whereas controlled exposures at 190 ppm-h were without effect for individuals not categorized as heavy drinkers. The following language was added for clarity: "This exposure information indicates that a 3-fold exposure reduction to the NOEC value produces an extreme toxic response in heavy drinkers, suggesting that an UF of 10 for intraspecies variability is protective of heavy drinkers."

	unexpected lifestyle practice of some among the populations being assessed in this risk evaluation. Without such documentation, one might consider it appropriate to expand the UF_H to 12-15 and the benchmark MOE to 12-15 from 10. As for the acute exposure scenarios, the Agency must provide adequate documentation that the 10X intra-human UF adequately covers the special populations that it acknowledges. Without such documentation, one might consider it appropriate to expand the range of UF_H to 12-15. The resulting noncancer chronic benchmark MOE, which would encompass the uncertainties related to interspecies toxicodynamic and intra-human variability and database deficiencies, would increase from 30 to 120 or 150 (UF_A x UF_H x UF_D = benchmark MOE: 3.16 x 12 x 3.16 = 120 or 3.16 x 15 x 3.16 = 150). EPA has identified specific subgroups with biological characteristics that make it likely that they will experience adverse effects from CCl4 at lower concentrations than healthy adults. To provide protection to these groups, a UF beyond the default intraspecies 10X factor should be applied, as EPA has previously done for other susceptible groups such as infants and children. The SACC should recommend that EPA apply a UF of 20X.	
SACC, 23, 30, 32, 43	**SACC COMMENTS: In favor of database UF** A Committee member commented that there appears to be an important data gap and uncertainty about what exposure level will protect a developing fetus for a pregnant woman exposed in the workplace.	There is no universal list of hazard data required when evaluating chemical risks under TSCA. Furthermore, for carbon tetrachloride, EPA has sufficient, reasonably available hazard information to conduct a risk evaluation and support the use of the chosen hazard endpoints. Therefore, EPA did not use a database UF in the carbon tetrachloride risk

	PUBLIC COMMENTS: In favor of database UF There are no studies that evaluate the potential for reproductive effects, a significant deficiency, given that men and women of active reproductive age are likely to be members of both the worker and ONU populations. A database deficiency UF >1X (at least 3X) should be incorporated when deriving the chronic noncancer benchmark MOE, raising it from the current agency choice of 30 to at least 100. The draft risk evaluation identifies developmental toxicity as an endpoint with limited data, and there is also no neurodevelopmental toxicity study on CCl4, an area of potential concern given its serious neurotoxic effects. No endocrine effects data are available either. Given the extent of these data gaps, we believe a UF of 10 is warranted. The paucity of any toxicology data on CCl4's effects by the dermal route of exposure, combined with the lack of dermal absorption studies, create a high level of uncertainty in EPA's assessment of dermal risks. EPA should add a UF of 10 to its current benchmark MOEs for dermal exposure of 100 (acute) and 30 (chronic). **PUBLIC COMMENTS: Against database UF** EPN sees no need for a database UF to be employed in the acute exposure assessments.	evaluation.
SACC	**SACC COMMENTS: Acute UF** • A Committee member commented that the NAS in their recommendations for operating procedures in the setting of AEGLs (NRC, 2001) provided more leeway in the choice of UFs than may be indicated by the Agency's own guidance. • EPA should consider adapting this type of decision	The following language was added to section 3.2.5, Dose Response Assessment: EPA applied a composite UF of 10 for the acute inhalation benchmark MOE, based on the following considerations: **1) Interspecies uncertainty/variability factor (UFA)**

	roadmap as described in Sections 2.5 and 2.6 in NRC (2001) in order to increase clarity and transparency when adopting UFs. • Another Committee member commented that while EPA used the UF of 10 for acute CNS depression, the AEGL committee determined that the value of 3 was sufficient. Therefore, EPA should clarify that the UF would protect against liver toxicity for all purposes. • A 12-fold intra-human variability was found in the quantities of hepatic microsomal CYP2E1 (Snawder and Lipscomb, 2000). For this reason, the Committee member questioned if the UF for intrahuman variability should be greater than 10 and suggested that a factor of 12 be used. Recommendation: Consider whether additional UFs are needed.	**of 1** Accounting for differences between animals and humans is not needed because the POD is based on data from humans **2) A default intraspecies uncertainty/variability factor (UFH) of 10** To account for variation in sensitivity within human populations due to limited information regarding the degree to which human variability may impact the disposition of or response to, carbon tetrachloride including reasonably available quantitative information on human variability in CYP2E1 enzyme in adults.
43	**PUBLIC COMMENTS: Cancer UF** EPA should consider adding a UF to its cancer risk estimates to acknowledge that they do not account for the multiple tumor types associated with CCl4.	EPA evaluated cancer risk from carbon tetrachloride and other chemicals using an approach consistent with the EPA Guidelines for Carcinogen Risk Assessment, thus and additional UF was not applied.
SACC	**SACC COMMENTS:** • EPA stated that the conservative assumptions used to derive PODs were likely to result in overestimation of risk. However, some Committee members disagreed with this statement. It was the opinion of some members, regarding mortality observed in the Wahlberg and Boman (1979) study (the only dermal study with an acceptable rating), that it was important to refrain from underestimating risk. • The Committee also noted that PODs could be erroneously calculated for acute occluded and non-	The description of uncertainties in dermal risk and dermal PODs were revised in the risk evaluation

	occluded dermal exposure. The Agency should address over- or underestimating risks prior to its determination. Recommendation: Re-evaluate the description of uncertainties in dermal risk after addressing the faulty calculations used in estimating the dermal POD.	
26	**PUBLIC COMMENTS:** To the extent that there are uncertainties in EPA's analysis, such uncertainties counsel in favor of a finding of unreasonable risk – EPA could as easily be underestimating the risk presented by these conditions of use as overestimating them. Uncertainty increases the chances of an unreasonable risk; it does not diminish them. Uncertainty, standing alone, does not justify a finding of no unreasonable risk when EPA's own analyses support a finding of unreasonable risk.	To determine whether or not a condition of use presents unreasonable risks, EPA incorporates assumptions based on information and judgment underlying the exposure scenarios. These assumptions, which include assumptions regarding PPE use, are described in the unreasonable risk determination for each condition of use, in section 5.2. It is important to note that the benchmarks for cancer and non-cancer risk estimates are not bright lines, and EPA has discretion to make unreasonable risk determinations based on other risk benchmarks or factors as appropriate. EPA uses the high-end exposure value when making its unreasonable risk determination in order to address uncertainties around PPE usage as well as to capture exposures for PESS. EPA is making its unreasonable risk determinations on the high-end exposure value for workers and consumers and either the high-end exposure value or central tendency for ONUs, depending on the data, and factoring in the uncertainties due to UF factors. Additionally, EPA makes an unreasonable risk determination and makes no determination on reasonable risk.
38	**PUBLIC COMMENTS:** By assuming extensive use of PPE, without any evidence that is the case, EPA leaves all workers exposed below the OSHA PEL subject to the voluntary whims of their employer, with no mandatory, enforceable duty under either OSHA or TSCA that workers be provided protection	For the purposes of determining whether or not a condition of use presents unreasonable risks, EPA incorporates assumptions regarding PPE use based on information and judgment underlying the exposure scenarios. These assumptions are described in the unreasonable risk determination for each condition of use, in section 5.2 of the

	against the risks posed by CCl4. Leaving workers in this void violates TSCA. EPA should revise the draft risk evaluation to address these issues and promptly take action to eliminate all of CCl4's unreasonable risks.	risk evaluation. Additionally, in consideration of the uncertainties and variabilities in PPE usage, EPA uses the high-end exposure value when making its unreasonable risk determination in order to address those uncertainties. EPA has also outlined its PPE assumptions in section 5.1 of the risk evaluation. Further, in the final risk evaluation for carbon tetrachloride, EPA has determined that most conditions of use pose an unreasonable risk to workers even with the assumed PPE.
Validity of confidence summaries		
SACC, 45	**SACC COMMENTS:** • A Committee member commented that the confidence summaries are appropriate as written, while also expressing the sentiment that it would be more useful to have confidence expressed in a more quantified manner. • Another member commented that, in general, there appears to be discrepancies between the types and levels of uncertainties described by the Agency, and the resulting levels of confidence. For example, high confidence relating to environmental risk appears overstated given the uncertainties described as related to environmental risks. Similarly, the high level of confidence for surrogate scenarios is not well justified. • Specific data inadequacies/uncertainty and assumption uncertainties are not carried through to confidence assessment of risk estimates. A formal process needs to be established, described, and consistently followed. Recommendations: (1) Section 4.5 of the risk evaluation should present a more detailed discussion of the links between uncertainties in exposure as well as hazard assessment, and the overall level of confidence assigned to each risk estimate; little was stated about uncertainties in	EPA considered the key assumptions and uncertainties described in section 4.4 when determining the overall confidence for the risk estimates. EPA updated the confidence rating for environmental receptors in Section 4.5.1 to "moderate" to reflect uncertainties associated with risk estimates, which are described in Section 4.1. In addition, a species sensitivity distribution was added in Appendix F.4, to explore sensitivity among the most sensitive taxonomic group, amphibians. Section 4.5 has been edited to include additional discussion of uncertainties.

	the hazard assessment as compared to the exposure estimation in this section of the draft risk evaluation; and (2) confidence statements on risk estimates should synthesize uncertainties in data and assumptions. • Additional clarity is needed on how the uncertainties propagate and are translated into the levels of confidence about risk the estimates, or in decisions about AFs. Recommendation: Consider scoring data and assumption uncertainty to derive a final confidence score. A Committee member indicated that the confidence rating of "high" presented in Section 3.1.2 (p. 97, lines 3108-3112) for risk to environmental receptors is not well supported when compared to statements on p. 160, lines 5173-5179, with respect to confidence in human health risk, and considering the complexity that includes environmental breakdown products and potential for indirect effects (*e.g.*, lack of invertebrate prey base), neither of which were evaluated. As a result, the confidence rating of "high" is not well supported. Raising UFs and/or AFs should correspond to raising confidence scores. **PUBLIC COMMENTS:** EPA should further explain what constitutes high confidence. For example, what were the results of the data quality evaluation, how many acute and chronic studies/data points were available, were all taxonomic groups represented (*i.e.*, fish, invertebrates, algae, etc.), were data consistent and comparable, what were the most sensitive species (a species sensitivity distribution would	

	be informative). At present, this section is lacking in information for the reader to confirm the conclusions in this section.	
Objectivity of assumptions and data		
SACC, 26, 38	**SACC COMMENTS:** • The Committee understood that monitoring and regulation of ambient air levels of CCl4 (and other similar volatile chemicals) fall under the purview of the CAA, but this fact should not excuse not including ambient CCl4 concentration in exposure calculations for workers, ONUs, and consumers. There are concerns that ambient CCl4 concentration values, in some locations, exposes workers, ONUs, and consumers living in these areas to greater risk for CCl4 and subsequent health effects. Recommendation: Include background exposures in the assessment for workers and ONUs or alternatively provide a more detailed justification why background exposures are not considered. **PUBLIC COMMENTS:** According to EPA, "[m]ost risk from NATA background concentrations is from carbon tetrachloride." EPA has failed to explain why it completely dismissed background exposures to CCl4 in the draft risk evaluation when the Agency has, very recently, calculated ongoing risk to the general population from background exposures to this chemical. EPA has not explained why, in direct contradiction to how EPA treated background exposures from HBCD to the general population, it chose to entirely ignore background exposures to CCl4.	Risks from background concentrations to carbon tetrachloride are assessed under the EPA NATA. The 2014 NATA reports a national ambient carbon tetrachloride concentration of 0.53 $\mu g/m^3$ and 3 in a million cancer risk. https://www.epa.gov/national-air-toxics-assessment/2014-nata-assessment-results#pollutant. EPA did not consider background exposure that workers using products containing carbon tetrachloride might be exposed to in addition to exposures from TSCA conditions of use. This may result in an underestimation of risk, and additional discussion of this underestimation has been added to the document in the Key Assumptions and Uncertainties section. Justification for not including background concentrations is presented in the final risk evaluation (see section 1.4.2.2).
26	**PUBLIC COMMENTS:** HSIA is the main trade association for manufacturers of halogenated solvents, such as CCl4, and, as such, it has a	The data gathering effort to support the risk evaluation was performed by literature searches and leveraging existing industry-specific information. HSIA data were provided as

	vested interest in EPA finding that the chemicals do not present unreasonable risk. This vested interest calls into question the reliability and completeness of the data voluntarily submitted by HSIA.	part of continuous industrial hygiene monitoring programs and were evaluated using the same criteria as other data sets. The reasonably available data readily attributable to manufacturing and processing of carbon tetrachloride were limited and contained their own deficiencies (such as the age of the studies, lack of discrete data points, and no metadata information) resulting in low quality ratings. Additionally, limited exposure data exists due to manufacturing, processing, and use restrictions enforced under the Montreal Protocol, CAA Title VI, and the Consumer Product Safety Commission ban.
26	**PUBLIC COMMENTS:** In its systematic review process, EPA rated the data that HSIA submitted in 2019 as 1.8, or "Medium." In doing so, EPA made some questionable decisions. First, EPA assigned the data a score of "1" for Geographic Scope apparently because the data come from U.S. facilities. However, it appears that the data represent only two manufacturing facilities (as EPA identifies them only as "Company A" and "Company B," p. 69), and it is far from clear that they are at all representative of the entire country as they comprise only a minority of facilities making or importing this chemical. Second, as EPA acknowledges in its systematic review, HSIA has not provided a standard description of the methods used to collect the data or to analyze the samples. EPA assigned the data HSIA submitted in 2019 a "3" for Methodology with the comment "not specified." However, because of EPA's approach to weighting criteria, which is inconsistent with best practices in systematic reviews, this "Low" score for Methodology has little impact on its overall score.	The assigned scores to both metrics are consistent with the approaches outlined in the Application of Systematic Review in TSCA Risk Evaluations document (https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/application-systematic-review-tsca-risk-evaluations). The geographic scope only considers whether the data were collected from site(s) within the United States to receive a "1" or "high" rating. Considerations of whether the data addresses variability between sites are considered when scoring the "variability and uncertainty" metric. This criterion received a score of "3" or "low" as the data does not address this topic. As indicated in the comment, the methodology scored a "3" or "low" as the sampling and analytical methods used were not specified. Companies A and B are the only companies manufacturing carbon tetrachloride.
Risk evaluation of potentially exposed or susceptible subpopulations		
SACC,	**SACC COMMENTS:**	Clarifying language on PESS has been added to section

38	• It was not clear as to why Section 2.5.1 appears to be abbreviated versus later discussions in Section 4.3, which describes potential PESS within workers and ONUs. • The draft risk evaluation lists the variables that define PESS in both Sections 3.2.5.4 and 4.3. However, each category is described to different extents, in some places extensively, in other places briefly, and occasionally not at all. For example, there are no descriptive discussions regarding subpopulations with pre-existing disease, beyond identifying the subpopulations as a category. The paragraph in lines 4964-4966 does not offer additional explanations in Section 4.3 due to workers and ONUs as being identified as PESS earlier in previous paragraphs. • The PESS section does not mention if intraspecies UFs of 10 were applied; UFs of 10X are generally used to account for variation among people and not for known PESS. • The Agency describes how a UF was used to account for variations of sensitivity, but it is not clear whether EPA did a separate assessment for these more susceptible individuals. It would seem that EPA is considering them as part of the workers and ONU groups, but this explanation is not clear in the document. • A Committee member noted that the discussion of PESS appears disjointed and not very compelling without a risk evaluation for susceptible populations. Recommendation: Consolidate explanation of PESS into one section and develop more protective guidelines for PESS.	3.2.5.4

	PUBLIC COMMENTS: Under TSCA, EPA must account for and protect not only exposed workers, but also those subpopulations who are most susceptible to a chemical's risks. The draft CCl4 risk evaluation fails to do so.	
SACC	**SACC COMMENTS:** • The data on cancer endpoints suggest that there may be differences with age (adults versus children for brain cancer, for example), race (Japanese Americans versus White Americans), and metabolic germline polymorphisms. None of this is discussed or analyzed in depth in this document. • There are novel genome-wide association studies (GWAS) studies that suggest genetic differences that may modulate acute exposure effects. These should be identified and discussed. Recommendation: The discussion on PESS should include subgroups and conditions identified in epidemiologic studies and in more recent GWAS research.	The brain cancer studies were all conducted in adult populations so there were no differences by age. While one of the studies (Nelson et al., 2012) reported increased risks within a cohort of Japanese American men, other studies reported increased risks among people from across the U.S., which did not suggest differences by race.
SACC	**SACC COMMENTS:** • Hereditary hemochromatosis is an autosomal recessive disorder that affects about 1 in 200-500 individuals. Those who are either homozygous or heterozygous for this condition should be included among the groups that would be more sensitive to CCl4-induced oxidative and peroxidative damage. • Another Committee member commented that the embryo and fetus (pregnant female workers) should be considered a PESS based on the neuroblastoma risk. Recommendation: Consider including and discussing individuals who are sensitive to oxidative damage and the embryo/fetus of pregnant female workers as PESS.	The following language was added to the PESS section: Heterogeneity in the human population distribution of microsomal enzymes metabolizing carbon tetrachloride has influence in the susceptibility to this chemical because metabolism is a hypothesized key event in carbon tetrachloride toxicity. Reasonably available quantitative information on the variation in human hepatic levels of the main metabolic enzyme, CYP2E1, demonstrates considerable intrahuman variability. For example (Lipscomb et al., 1997) reported a sevenfold range in activity of CYP2E1 among hepatic microsomal samples from 23 subjects. Snawder and Lipscomb (Snawder and Lipscomb, 2000) demonstrated 12-fold differences in CYP2E1 protein content between the highest and lowest samples from 40 samples of microsomes

		from adult human liver organ donors. Consideration of this PESS quantitative information is incorporated in the UFs used in the risk characterization. Qualitative information on susceptibility could not be incorporated in the UFs.
32, 38, 43	**PUBLIC COMMENTS:** There are two significant ways in which the draft risk evaluation uses insufficiently protective UFs and understates risks as a result. "[C]ases of acute toxicity from occupational exposures indicate that heavy drinkers are more susceptible to carbon tetrachloride and this observation has been verified in numerous animal studies." In addition, "reduced kidney function and increased CYP3A activity in the liver (indicated by animal studies) suggest that older populations could be at greater risk of carbon tetrachloride-associated kidney damage." In its draft risk evaluation, EPA identified "human subpopulations that may have greater susceptibility to carbon tetrachloride than the general population," including moderate to heavy alcohol users, people with preexisting liver disease, and populations with certain genetic polymorphisms. However, EPA does not evaluate the risks facing these specific subpopulations, but instead relies on a default intraspecies UF to account for all of them. For instance, EPA does not consider alcohol consumption rates within the exposed worker population or separately adjust its risk calculations to account for these susceptibilities. Under TSCA, EPA must calculate risks for these PESS, or at a minimum demonstrate that its chosen UF is sufficient to account for all such populations.	Section 3.2.5.4 of the final risk evaluation states that the variability in the adverse response to carbon tetrachloride exposure in relation to alcohol consumption is emphasized by the fact that an in a heavy drinker whereas controlled exposures at 190 ppm-h were without effect for individuals not categorized as heavy drinkers. The following language was added for clarity: This exposure information indicates that a 3-fold exposure reduction to the NOEC value produces an extreme toxic response in heavy drinkers, suggesting that a UF of 10 for intraspecies variability is protective of heavy drinkers.
30	**PUBLIC COMMENTS:** This draft risk evaluation includes the assessment of risk to workers and ONUs from acute and chronic inhalation and	EPA did not identify any legacy uses or associated disposals for carbon tetrachloride. EPA did not assess exposures from legacy disposals, or disposals that have already occurred,

	dermal exposures. However, neither pregnant women nor male workers considering a family nor the general population, which also includes infants and young children, have been specifically addressed. This becomes particularly important once the risk evaluation is updated to include the analysis of legacy consumer conditions of use.	because they are not considered conditions of use. Clarifying language about what pathways are under the jurisdiction of other EPA-administered statutes has been added to Section 1.4.3 of the Risk Evaluation. EPA did not evaluate risks to the general population from any conditions of use and the unreasonable risk determinations do not account for exposures to the general population. Additional details regarding the general population are in Section 1.4.3. The products available for purchase by consumers are not expected to contain measurable amounts of carbon tetrachloride because carbon tetrachloride is not used in the manufacturing of the actual products. Trace levels of carbon tetrachloride in the chlorinated substances used to manufacture the products are expected to volatilize during the product manufacturing process. Furthermore, background concentrations to carbon tetrachloride are assessed under the EPA NATA. Therefore, consumer conditions of use were removed from the risk evaluation in the exercise of EPA's discretionary scoping authority under TSCA sec. 6(b)(4)(D). EPA does account for exposures to potentially exposed or susceptible subpopulations (PESS) by using the high-end exposure value when making its unreasonable risk determination for workers.
38	**PUBLIC COMMENTS:** The statute specifically defines PESS to include "workers," reflecting Congress's intent that EPA evaluate and address occupational risks under TSCA.	EPA identified the following potentially exposed or susceptible subpopulations based on their greater exposure to carbon tetrachloride: workers and ONUs. TSCA section 3(12) lists examples of "potentially exposed or susceptible subpopulations" but neither that provision nor

		TSCA section 6(b) specifies subpopulations that must be considered PESS in any given risk evaluation. EPA therefore has the discretion to identify PESS that are relevant to a risk evaluation.
26	**PUBLIC COMMENTS:** Workers at any facility – whether small, medium, or large – where use of effective PPE cannot be thoroughly documented should be considered vulnerable subpopulations and the risk they face be specifically assessed. For these subpopulations, EPA must determine risk based on exposures without assuming any use of PPE.	PPE use expectation is applicable to all facilities (OSHA regulations cover large and small facilities). EPA has recognized in the draft and final risk evaluations OSHA's hierarchy of controls and recognized that there can be reliability issues associated with PPE. EPA's risk evaluation characterizes risks with and without PPE considerations, with considerations of engineering and administrative controls. Additionally, in consideration of the uncertainties and variabilities in PPE usage, EPA uses the high-end exposure value when making its unreasonable risk determination in order to address those uncertainties. EPA has also outlined its PPE assumptions in section 5.1.
26, 41, 42	**PUBLIC COMMENTS:** As part of this analysis, EPA should identify people living near all disposal sites containing CCl4 as PESS. These groups include (but are not limited to) those living near Superfund or NPL sites. To be clear, many disposal sites are associated with activities that reflect ongoing or prospective manufacturing, processing, distribution, or use, so EPA must also analyze those disposals and disposal sites and populations living in proximity to them. Additionally, EPA should include all communities living near facilities that report releases of CCl4 under TRI. In order to make an accurate risk characterization of tribal communities, EPA needs to consider releases of CCl4 from landfills. In the case of many tribal and rural communities, the disposal site may be in close proximity to	Clarifying language on exposure pathways and risks under the jurisdiction of other EPA-administered statutes have been added to section 1.4.3 of the final risk evaluation document. EPA did not identify any legacy uses or associated disposals for carbon tetrachloride. EPA did not assess exposures from legacy disposals, or disposals that have already occurred, because they are not considered to be "conditions of use."

	residents, may be unlined, may be open access, and may include open burning as a management practice, all of which present multiple exposure pathways and routes for intake and uptake. It cannot be assumed that all CCl4 product disposal would be at Subtitle C landfills. For example, there is not a single Subtitle C landfill in the State of Alaska. The multiple exposure scenarios associated with proximity to unlined disposal site releases to environmental media must be analyzed for both individual exposures and the cumulative exposures tribal members face from their customary and traditional tribal lifeways (inhalation, dermal, ingestion). EPA provides no analysis of whether those living in proximity to the conditions of use are at greater risk due to greater exposure. EPA should analyze these exposures and should analyze these potentially exposed subpopulations. EPA's failure to consider this relevant aspect of the problem is arbitrary and capricious.	
42	**PUBLIC COMMENTS:** Tribal lifeways can lead to chronic exposures to toxins in the environment, due to the much longer duration and higher frequency of exposures tribal people may experience, as well as the higher cumulative dose from multiple exposure pathways (*i.e.*, differences in diet, housing, worker safety, and water use). Tribes must be considered as a sensitive subpopulation under TSCA. NTTC has in previous comment letters informed EPA in detail about the unique characteristics of disposal sites on tribal lands and in tribal communities and we are able and willing to provide extensive photographic and narrative	Clarifying language about what pathways are under the jurisdiction of other EPA-administered statutes has been added to Section 1.4.3 of the Risk Evaluation. EPA did not identify any legacy uses or associated disposals for carbon tetrachloride. EPA did not assess exposures from legacy disposals, or disposals that have already occurred, because they are not considered to be "conditions of use." EPA did not evaluate risks to the general population from any conditions of use and the unreasonable risk determinations do not account for any risks to the general population. Additional details regarding the general population are in Section 1.4.3. Because "the term 'potentially exposed or susceptible

	evidence that exposure through disposal is very likely for tribal people.	subpopulation' means a group of individuals within the general population identified by the Administrator who, due to either greater susceptibility or greater exposure, may be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture, such as infants, children, pregnant women, workers, or the elderly," EPA believes that the statutory directive to consider potentially exposed or susceptible subpopulations (PESS) and the statutory definition of PESS inherently include tribes. Therefore, the UF applied to account for PESS do cover tribal exposures. EPA did not consider background exposure that workers using products containing carbon tetrachloride might be exposed to in addition to exposures from TSCA conditions of use. This may result in an underestimation of risk, and additional discussion of this underestimation has been added to the document in the Key Assumptions and Uncertainties section.
42	**PUBLIC COMMENTS:** The SACC has previously stated that EPA must consider all exposure routes and give "special consideration to specific populations (*e.g.*, tribal, arctic inhabitants, etc.) who depend on fish as a major source of food because of cultural considerations and provide some quantitative sense of how much extra risk exists for these populations. In considering special and susceptible population exposures, more consideration needs to be given to populations with specific preexisting conditions, such as metabolic disease and obesity, as well as to tribal, ethnic and other subpopulations that depend heavily on potentially contaminated foods, such as Native American subsistence fishers."	Clarifying language about what pathways are under the jurisdiction of other EPA-administered statutes has been added to Section 1.4.3 of the Risk Evaluation. EPA does account for exposures to potentially exposed or susceptible subpopulations (PESS) by using the high-end exposure value when making its unreasonable risk determination for workers. Because "the term 'potentially exposed or susceptible subpopulation' means a group of individuals within the general population identified by the Administrator who, due to either greater susceptibility or greater exposure, may be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture, such as infants, children,

	Clearly, tribes experience exposures even where responsibility rests on other environmental statutes (RCRA, SDWA, CWA CAA) and NTTC strongly urges EPA to comply with their statutory obligation to consider all exposures, particularly for susceptible and highly exposed populations, such as tribes. NTTC has expressed concern at the paucity of data on tribal risks, as well as the observation that tribal people are absent from or underrepresented in EPA's risk evaluations and proposed actions. It is well documented in the scientific literature that Native Americans experience significant health disparities from the general population and the practice of leaving them out of any protections will only contribute to further health disparities. NTTC urges EPA to include consideration of Tribal data that may be submitted by the Tribe that produced it. Where data are not available, modeling should be employed so that all significant Tribal exposures are captured.	pregnant women, workers, or the elderly," EPA believes that the statutory directive to consider potentially exposed or susceptible subpopulations (PESS) and the statutory definition of PESS inherently include tribes. In addition, based on its physical-chemical properties, carbon tetrachloride does not partition to lipid or bioaccumulate in fish (BCF is estimated at 40, whereas the threshold for bioaccumulative chemicals is 1,000). Therefore, elevated fish consumption by individuals (*i.e.*, such as indigenous populations) is not a factor for carbon tetrachloride susceptibility. Residual concentrations of carbon tetrachloride in surface waters not used for drinking water are also regulated via the CWA Ambient Water Quality Criteria for human health consumption of water and organisms (0.4ug/L). CWA(a)(1).
42	**PUBLIC COMMENTS:** The SACC also recommended that "the context of the assessment would be improved by including a graphic similar to the one presented by the National Tribal Toxics Council at the public meeting, that illustrates exposure routes for potentially sensitive or highly exposed populations" (reference to the conceptual model).	EPA appreciates this suggestion, which will be considered for future risk evaluations.
42	**PUBLIC COMMENTS:** In this draft risk evaluation, EPA limited its analysis to only considering people who have higher susceptibility to CCl4 due to genetic polymorphism in its metabolizing enzymes. However, other than the consideration of worker	Section 3.2.5.4 explains how PESS quantitative information is incorporated in the UFs used in the risk characterization. Qualitative information on susceptibility could not be incorporated in the UFs.

	and ONU exposures, EPA did not consider whether any subpopulations might face greater risk due to greater exposure to CCl4. EPA must consider and analyze each of these types of subpopulations, as mandated by the Lautenberg Act.	
Risk evaluation of workers with PPE		
SACC, 23, 26, 30, 32, 38, 42, 43	**SACC COMMENTS:** EPA is not adequately considering the hierarchy of controls in occupational hygiene and is emphasizing the last step, which is PPE. Hard empirical evidence for assumed levels of PPE efficacy linked to the conditions of use being described is not provided. The Agency relies upon generic tabulated values. This approach entails substantial uncertainty. EPA is not adequately considering issues of training, availability of appropriate materials, and human factors in compiling tables of PPE efficacy. Discussion on pp. 62-63 of the draft risk evaluation describes results of a NIOSH survey of U.S. employers regarding the use of respiratory protective devices between August 2001 and January 2002 that suggested that full adherence to best PPE practice is likely a minority occurrence. Estimation of central tendency and high-end exposures with assumption that high degrees of protection are routinely achieved is problematic. Recommendation: Provide a brief description of the rationale for linking the information on occupational exposure control to the decision to apply respirator and glove PFs.	OSHA's hierarchy of controls is a method for eliminating workplace hazards. EPA will manage unreasonable risks presented by chemical substances when the Agency undertakes regulatory action for conditions of use determined to have unreasonable risk. Utilization of the hierarchy of controls to recommend or require risk management actions in the risk evaluation would be premature and inappropriate. Assumed PPE is reflected by the type of use, whether industrial, commercial, or consumer, and the anticipated presence of an industrial hygiene program. EPA does not assume that the use of SDSs are sufficient to ensure PPE use and EPA does not make PPE use assumptions based on SDSs. The OSHA regulations at 29 CFR 1910.132 require employers to assess a workplace to determine if hazards are present or likely to be present which necessitate the use of PPE. If the employer determines hazards are present or likely to be present, the employer must select the types of PPE that will protect against the identified hazards, require employees to use that PPE, communicate the selection decisions to each affected employee, and select PPE that properly fits each affected employee. OSHA has established a PEL of 10 ppm (8-hour TWA) for carbon tetrachloride at 29 CFR 1910.1000. However, as noted on OSHA's website, "*OSHA recognizes that many of its PELs are outdated and inadequate for ensuring protection of worker health. Most of OSHA's PELs were issued shortly after adoption of the Occupational Safety*

	PUBLIC COMMENTS: The CCl4 risk evaluation provides a detailed discussion of the role of PPE in workplace protection strategies (*i.e.*, hierarchy of controls), which demonstrates that PPE are not a substitute for more effective controls on workplace exposure and that there is considerable uncertainty about whether PPE is consistently used even where legally required. Thus, to rely entirely on PPE without first requiring engineering controls and other protections – as EPA effectively does in the CCl4 risk evaluation – is contrary to accepted principles of worker protection. EPA relies on OSHA's Hazard Communication Standard to support its "expect[ation]" that workers will be provided "appropriate PPE consistent with the applicable SDSs in a manner adequate to protect them." However, the Hazard Communication Standard merely requires the provision of SDSs, not PPE, and OSHA has made clear that employers are under no obligation to follow the recommendations in an SDS. In the absence of such a requirement, there is no basis for EPA's assumption that the Hazard Communication Standard will result in the uniform use of appropriate PPE. The information and recommendations included in SDSs are based on manufacturers' judgment. As a result, they are often vague and inconsistent. Further, SDS recommendations are not binding on employers. EPA has no basis for assuming that specific glove PFs in its draft risk evaluation.	*and Health (OSH) Act in 1970, and have not been updated since that time*." OSHA provides an annotated list of PELs on its website, including alternate exposure levels. For carbon tetrachloride, the alternates provided are the California OSHA PEL of 2 ppm and the ACGIH TLV of 5 ppm. (https://www.osha.gov/dsg/annotated-pels/tablez-1.html). EPA agrees that there are challenges associated with use of PPE; they are described in Section 5.1.1.3. By providing risk estimates that account for use of PPE, EPA is not recommending or requiring use of PPE. Rather, these risk estimates are part of EPA's approach for developing exposure assessments for workers that relies on the reasonably available information and expert judgment. When appropriate, in the risk evaluation, EPA will use exposure scenarios both with and without engineering controls and/or PPE that may be applicable to particular worker tasks on a case-specific basis for a given chemical. Again, while EPA has evaluated worker risk with and without PPE, as a matter of policy, EPA does not believe it should assume that workers are unprotected by PPE where such PPE might be necessary to meet federal regulations, unless it has evidence that workers are unprotected. For the purposes of determining whether or not a condition of use presents unreasonable risks, EPA incorporates assumptions regarding PPE use based on reasonably available information and professional judgment underlying the exposure scenarios. These assumptions are described in the unreasonable risk determination for each condition of use, in section 5.2. In the case of carbon tetrachloride, which is manufactured, processed, and used in industrial settings,

	EPA assumes that workers will not only be provided with appropriate respirators with an average PF up to 50 and chemical-resistant gloves with a PF up to 20, but will receive the training, fit testing, and medical evaluations required to ensure proper respirator use. Does the draft risk evaluation provide adequate support for those assumptions? EPA assumes that workers exposed to CCl4 will wear respirators. These assumptions are legally and factually baseless. Small facilities are much less likely to require routine and effective use of PPE or to employ engineering controls, such as closed systems. Smaller businesses and facilities are the norm in Indian Country, including Alaska Native villages, and they are subject to OSHA exemptions to the Respiratory Protection Standard, as well as to reporting and inspection requirements. Self-employed workers are also exempt from many OSHA requirements and self-employment is common in tribal communities. For accurate risk characterization of tribal members, NTTC would like to see a risk determination for workers and ONUs, both self-employed and in small businesses, that incorporates OSHA's exemptions and practical exceptions. In these communities, take-home exposures are also very likely. CCl4 is produced and used by thousands of workers across a range of different sectors. Even within a given condition of use (*e.g.*, disposal and waste handling), there often are a wide range of employers and workplaces. However, EPA arbitrarily assumes that all workers will be provided with, and will use, PPE, without any supporting evidence. EPA must make risk determinations about CCl4 use under the	where there are typically strong industrial hygiene programs that include training and oversight, EPA believes that it is reasonable to assume a PF of 20 for dermal protection (gloves) and APF of 50 for inhalation protection (respirators). Additionally, in consideration of the uncertainties and variabilities in PPE usage including the duration of PPE usage, EPA uses the high-end exposure value when making its unreasonable risk determination in order to address those uncertainties. EPA has also outlined its PPE assumptions in section 5.1. Further, in the final risk evaluation for carbon tetrachloride, EPA has determined that most conditions of use pose an unreasonable risk to workers even with the assumed PPE.

	foreseen (and known) circumstances, assuming such respirators are not worn. Mendeloff et al. (2013) noted that "the pattern of noncompliance across industries mostly mirrored the survey findings about the prevalence of requirements for respirator use." Based on this study EPA concluded "The likelihood of respirator use may not be widespread or effective" (p. 63). EPA identifies no data concerning the use of respirators by workers exposed to CCl4, and it acknowledges "the likelihood of respirator use may not be widespread or effective." In the absence of chemical specific data, EPA relies on a generic 2003 NIOSH survey, which reports that among the small fraction of employers that require respirators, most do not conduct the planning, training, and testing required to ensure that respirators are serving their intended function. These data show wide gaps in use of appropriate respirators and measures of effectiveness. EPA has previously acknowledged that "not all workers may be able to wear respirators." In particular, EPA explained that "[i]ndividuals with impaired lung function due to asthma, emphysema, or chronic obstructive pulmonary disease … may be physically unable to wear a respirator." Workers' facial hair, including beards and sideburns, can also interfere with the seal of a respirator, rendering it ineffective. Other workers cannot wear respirators because they "may also present communication problems, vision problems, worker fatigue, and reduced work efficiency." OSHA and NIOSH have similarly found that respirators can cause discomfort, skin irritation, heat	

	stress, communication difficulties, and vision limitations, and that they often create other hazards for workers, such as trips, falls, and "struck by" hazards. NIOSH has found that respirator programs often provide inadequate protection even where respirator use is legally required and there is serious doubt whether respirator use at many facilities is consistent, reliable, and protective. There is no basis for EPA to assume that employers will voluntarily exceed the OSHA standard and provide additional respiratory protection to eliminate the risks below the PEL. EPA proposes to determine that CCl4's risks to workers are not unreasonable where the "expected" use of respirators and gloves would reduce exposures to levels that provide "acceptable" MOEs and cancer risk levels as compared to EPA's benchmarks. However, as the SACC has repeatedly underscored and EPA's draft evaluations recognize, this "expectation" of universal PPE use is not grounded in data, departs from established workplace protection policy, and is contrary to the realities of worker exposure to unsafe chemicals. Risk estimates should be presented without the use of PPE as reasonable worst case. This will result in a determination that workers are at unreasonable risk from CCl4 (cancer and noncancer risks). The worker protection measures necessary to protect workers from this risk should be in risk management rulemaking under TSCA section 6(a).	
SACC	**SACC COMMENTS:** Recommendation: EPA should replace the assumed APFs in Table 4-13 with data-based estimates. If no reliable estimates can be developed, only risk estimates assuming	EPA considers ONUs to be a subset of workers for whom the potential inhalation exposures may differ based on proximity to the exposure source. EPA assumed an absence of PPE for ONUs, since ONUs do not directly handle the chemical and

	no PPE use should be presented, with appropriate caveats in the discussion. • SACC members noted that ONU exposures were deemed unreasonable, but worker exposures were deemed reasonable. Workers are assumed to be exposed both via inhalation (in higher concentration environments than ONUs) and by dermal contact to liquids (while ONUs are not). The counterintuitive finding that ONUs are at higher risk highlights the assumption made that workers routinely have access to appropriate PPE and use it effectively. Several SACC members expressed doubts regarding this assumption. (It was noted that the finding of no unreasonable risk to workers via dermal contact to liquid was an artifact of an error in calculating the cancer slope factor; see charge question 4.)	are instead doing other tasks in the vicinity of carbon tetrachloride use. For dermal exposures, because ONUs are not dermally exposed to carbon tetrachloride, dermal risks to ONUs were not assessed. Based on comments received on the draft risk evaluation, EPA was able to evaluate ONU inhalation exposures separately from workers for several carbon tetrachloride conditions of use, including domestic manufacturing. Consistent with the way that unreasonable risk determinations are made for workers, for these conditions of use with ONU-specific exposure estimates, EPA uses the high-end exposure value when making its unreasonable risk determinations in order to capture exposures for PESS. For the rest of the conditions of use, the difference between ONU exposures and workers directly handling the chemical cannot be quantified. EPA assumed that, in most cases, ONU inhalation exposures are lower than inhalation exposures for workers directly handling the chemical substance. For inhalation exposures, to account for those instances where, based on EPA's analysis, the monitoring data or modeling data for worker and ONU inhalation exposure could not be distinguished, EPA considered the central tendency risk estimate when determining ONU risk. In the risk evaluation for carbon tetrachloride, EPA used the high-end exposure value when considering worker risks in order to address the uncertainties and variability in PPE usage. For inhalation exposures, EPA, where possible, estimated ONU exposures and described the risks separately from workers directly exposed. To account for those instances where, based on EPA's analysis, the monitoring data or

		modeling data for worker and ONU inhalation exposure could not be distinguished, EPA considered the central tendency risk estimate when determining ONU risk. EPA considered the high-end no PPE scenario within each OES as the sentinel exposures for workers. In presenting the inhalation results, high intensity use was characterized by the model iteration that utilized the 95th percentile duration of use and mass of product used and the maximum weight fraction derived from product specific SDS, when available. Dermal exposures for high intensity use were characterized by the model iteration that utilized the 95th percentile duration of use and maximum weight fraction.
SACC	**SACC COMMENTS:** There are gaps between the description of the exposure control hierarchy and the application of the PPE PFs that reduce clarity. The risk evaluation should provide 1-2 paragraphs describing the decision process between acknowledgement of guidelines for exposure control and the application of PFs for PPE. A Committee member indicated that the description of exposure controls, PPE, and the effectiveness of PPE should also be briefly summarized in the risk characterization, even if it is discussed in detail elsewhere in the document.	See the Executive Summary, updated Risk Characterization (Section 4), and updated Risk Determination (Section 5) for more clarification on how these sections support each other and how new information submitted to or obtained by EPA following publication of the draft risk evaluation is incorporated.
SACC	**SACC COMMENTS:** The Committee is concerned about the use of respirator PFs, particularly for exposures for manufacturing and processing as reactant/intermediate (8- and 12-hour TWA). Even though EPA estimated high-end chronic inhalation exposures with noncancer MOEs below the benchmark and cancer risks greater than the benchmark,	EPA did assess the risk to workers in the absence of PPE and with PPE; those risk estimates are in Tables 4-7 through 4-13 in Section 4, Risk Characterization. EPA considers each condition of use and uses exposure scenarios with and without PPE that may be applicable to particular worker tasks on a case-specific basis for a given

	EPA drew a conclusion that there was no unreasonable risk in any of the manufacturing scenarios because of the exposure reductions expected as a result of use of respirators, which lead to MOEs greater than the benchmark MOE (Section 4.2.8, p. 158, Table 4-13). In a similar manner, there were cancer risks above the cancer risk benchmark for the high-end exposures for the additive, processing agent/aid, import and repackaging, specialty uses-Department of Defense (DoD), and disposal/recycling conditions of use, but EPA also accounted for the use of respirator PFs to conclude that the cancer risk was below the benchmark.	chemical. For the purposes of determining whether or not a condition of use presents unreasonable risks, EPA incorporates assumptions regarding PPE use based on information and judgment underlying the exposure scenarios.
SACC	**SACC COMMENTS:** EPA does not discuss glove life/replacement when faced with chemical and physical challenges.	Proper care, maintenance, useful life and disposal of PPE are recommended by OSHA. Several OSHA citations included in the risk evaluation document indicate recommended practices. The glove replacements are generally included in the industry-specific health and safety plan. These discussions are not within the scope of risk evaluation.
SACC	**SACC COMMENTS:** Recommendation: EPA should provide sufficient detail on the use of the conceptual model in Cherrie et al. (2004) so that a reader could reproduce the values reported in Table 2.3. • If glove PFs depend upon flux and time, an explanation is needed as to why the values reported in Table 2.3 depend on neither.	The citations of relevant peer-reviewed articles are included in the risk evaluation document. The Table 2-5 (Table 2-3 in the previous version of the draft risk evaluation document) includes the cited reference.
SACC	**SACC COMMENTS:** A Committee member commented that any use of glove PFs listed in various tables or in discussion should clearly reference OSHA guidelines.	The relevant source of the glove PFs cited as footnote of the Table 2-5 as suggested.
SACC	**SACC COMMENTS:** A Committee member stated as part of its Risk21® effort, the Health and Environmental Sciences Institute (HESI)	EPA appreciates the information on different tools for conveying risk with and without PPE. As EPA continually refines its risk evaluations, it will consider this tool as a

	developed a graphic that may prove useful in demonstrating risks with and without the use of PPE. The graphic can be generated using a web-based tool available from the risk21.org web site.	possible option.
39	**PUBLIC COMMENTS:** HSIA submitted a description of the industrial hygiene practices at CCl4 production facilities, including details on tasks by exposure groups and generalized PPE requirements (EPA-HQ-OPPT-2019-0499-0029).	EPA has reviewed industrial hygiene practice reports on carbon tetrachloride submitted by the commenter as well as the details on the tasks by exposure groups and generalized PPE requirements submitted by the commenter.
26, 32, 38, 39, 43	**PUBLIC COMMENTS:** EPA's assessment of dermal exposure likely underestimates exposure. EPA does not have any data on glove use and efficacy, which is necessary to accurately assess dermal exposure. EPA acknowledges that gloves are likely to provide only limited protection from CCl4, given that the chemical can break through gloves made of certain materials. EPA recognizes the potential for occlusion, whereby glove use can increase skin exposure (p. 60). However, the dermal exposure estimates do not account for occluded conditions. EPA's document provides contradictory discussion of occlusion for CCl4. EPA appears to acknowledge the limitations of gloves and their potential to increase skin absorption, but then to simply assume that gloves actually provide preset levels of protection over no gloves – regardless of the potential for occlusion – without citing any evidence to support these values. The premise seems to be that if the most protective gloves potentially available can be assumed to provide a PF that reduces risk to below the benchmark, then EPA can conclude that there is no unreasonable risk. This approach will allow clear risks to occur whenever a worker uses anything less than the most	The occlusion, no gloves use and gloves use with various PFs have been discussed in "10 CCl4 Supplemental File Engineering Report" that is attached with the final risk evaluation document. In addition, the revised risk evaluation has been updated with real word usage scenarios with citations of peer-reviewed publications (see Section 2.4.1.5 - Consideration of Engineering Controls and Personal Protective Equipment).

	protective gloves (or no gloves), or when there is occlusion; these scenarios are quite likely to occur in the real world. The extent to which the preconditions for effective glove use are in fact followed in workplaces is highly uncertain. Overall, EPA concedes that it "does not know the actual frequency, type, and effectiveness of glove use in specific workplaces of the occupational exposure scenarios." The Agency assumes fixed PFs of 5, 10, and 20X, which do not appear to be supported by any empirical data that account for the complexities of glove use in the real world. EPA should revise the CCl4 risk evaluation so that its unreasonable risk determinations for workers are based on workplace exposure levels in the absence of PPE. Where unreasonable risk is demonstrated, PPE, along with other worker protection measures, should be considered in determining how best to eliminate the unreasonable risk.	
23, 26, 38	**PUBLIC COMMENTS:** The draft risk evaluation states that, because CCl4 "is a skin irritant and sensitizer," workers will be "persuaded on their own (in addition to the workplace industrial hygiene program and OSHA regulations) to wear gloves when handling the chemical." EPA does not explain how workers, many of whom are exposed to chemicals other than CCl4, will be able to identify the specific source of their rash or skin irritation, in order to identify the appropriate PPE. Nor does EPA indicate how workers who are able to diagnose their own injuries will be assured access to the proper type of protective equipment, which their employers may or may not supply.	The language has been replaced with the following: "carbon tetrachloride is identified and labeled as a skin irritant and sensitizer, which suggests that workers are less likely to not be wearing gloves when handling the chemical."
38	**PUBLIC COMMENTS:**	EPA must evaluate the conditions of use it expects to consider under TSCA in the risk evaluation and determine

	The Benzene decision has no bearing on EPA's duty to identify and manage unreasonable risks under TSCA. Consistent with NIOSH recommendations, EPA should reduce exposure to occupational carcinogens such as CCl4 "as much as possible," the extent of which should be decided during risk management and not during risk evaluation.	whether the condition of use presents unreasonable risk. If necessary, any risk management activities will only occur after EPA has completed the risk evaluation. The standard cancer benchmarks used by EPA and other regulatory agencies range from 1 in 1,000,000 to 1 in 10,000 (*i.e.*, $1x10^{-6}$ to $1x10^{-4}$) depending on the subpopulation exposed. EPA, consistent with 2017 NIOSH guidance, used $1x10^{-4}$ as the benchmark for the purposes of unreasonable risk determinations for individuals exposed to carbon tetrachloride in industrial and commercial work environments, including workers and ONUs. $1x10^{-4}$ is not a bright line and EPA has discretion to make unreasonable risk determinations based on other benchmarks as appropriate. See section 5.1.1.2 of the risk evaluation for additional information. In addition to assessing the cancer risk using a linear extrapolation approach and comparing the results to the standard cancer benchmark of 1×10^{-4}, EPA also assessed cancer risk using a threshold approach. Based on the threshold approach, EPA identified MOEs for cancer risks. EPA used both the risk estimates derived from the linear extrapolation approach and the MOEs derived from the threshold approach for the unreasonable risk determinations for individuals exposed to carbon tetrachloride.
26, 38	**PUBLIC COMMENTS:** By assuming extensive use of PPE at the risk evaluation stage, EPA also conflates risk evaluation with risk management. TSCA requires EPA to complete a risk evaluation and to make a determination of unreasonable risk before it considers how such risks may be managed.	Per the statute (see TSCA section 6(b)(4)(A)) and the implementing regulations for risk evaluations (40 CFR part 702, subpart B), EPA must make the unreasonable risk determination at the time of the risk evaluation. Upon finding unreasonable risk, EPA will apply risk management actions to the extent necessary so that the chemical no longer presents

	PPE is a risk management tool, albeit a poor one that may be used only when preferable options are not available. As such, PPE may only be considered, if at all, during the risk management stage when it can be weighed against more effective means of risk reduction.	such risk, in accordance with TSCA section 6(a). EPA considers the uncertainties associated with each condition of use, and how the uncertainties may result in a risk estimate that overestimates or underestimates the risk. Based on such analysis, EPA determines whether or not the identified risks are unreasonable. Such consideration carries extra importance when the risk estimates are close to the benchmarks for risks from acute and chronic non-cancer health effects and cancer.
38	**PUBLIC COMMENTS:** EPA notes that "engineering controls" should be "the primary means to control air contaminants" such as CCl4. However, because EPA assumes extensive respirator use to avoid unreasonable risk determinations, EPA will never proceed to the risk management stage where it can consider whether other, more cost-effective control options exist. This is particularly true with a chemical such as CCl4, which requires respirators with PFs up to 50. Such respirators have significant costs, both in the ability of workers to wear them while doing their jobs safely, and in the expense to employers of ensuring their comprehensive respirator program is adequate.	OSHA's hierarchy of controls is a method for eliminating workplace hazards. EPA will manage unreasonable risks presented by chemical substances when the Agency undertakes regulatory action for conditions of use determined to have unreasonable risk. Utilization of the hierarchy of controls to recommend or require risk management actions in the risk evaluation would be premature and inappropriate.
Other aspects of the human health risk characterization		
SACC	**SACC COMMENTS:** • Consumer exposures were not evaluated. This is justified by the fact that there are several indoor, outdoor, and personal monitoring studies demonstrating low-level concentrations of CCl4. • The risk evaluation should include a table and a brief discussion of these data to provide a more objective context for its decision not to evaluate risk for consumers, and for contrasting with occupational	The Consumer Product Safety Commission (CPSC) banned the use of carbon tetrachloride in consumer products (excluding unavoidable residues not exceeding 10 ppm atmospheric concentration) in 1970. As a result of CPSC's ban, EPA does not consider the use of carbon tetrachloride-containing consumer products produced before 1970 to be known, intended, or reasonably foreseen. In accordance with the CPSC ban, carbon tetrachloride is not identified in the California Air Resources Board consumer product database

	exposures. Recommendation: The assertion of no significant use in consumer products should be supported by a more specific description of the documentation used by EPA to arrive at its conclusion. Improve the discussion and summarize the data supporting the decision to exclude consumer exposures from this evaluation. Tabulate ambient air levels for perspective in assessing consumer background exposures.	nor the Washington State Product Testing Data list or the State of Vermont list of Chemicals in Children's Products and no consumer uses are listed in the CDR. As stated in the Problem Formulation, EPA determined after additional public outreach, literature searches and other reasonably available information, the consumer uses of carbon tetrachloride that were initially identified in the Scope document (*i.e.*, commercially available aerosol and non-aerosol adhesives/sealants, paints/coatings, and cleaning/degreasing solvent products) only have the potential for negligible exposure. Carbon tetrachloride is not a direct reactant or additive in the formulation of solvents for consumer use in cleaning and degreasing, adhesives and sealants or paints and coatings. Trace levels of carbon tetrachloride in the chlorinated substances used to manufacture the products are expected to volatilize during the product manufacturing process. Risks from background concentrations to carbon tetrachloride are assessed under the EPA NATA. The 2014 NATA reports a national ambient carbon tetrachloride concentration of 0.53 $\mu g/m^3$ and 3 in a million cancer risk. https://www.epa.gov/national-air-toxics-assessment/2014-nata-assessment-results#pollutant

Content and Organization
Charge Question 6.1: Please provide suggestions for improving the clarity of the information presented in the draft risk evaluation. **Charge Question 6.2:** Is the draft risk evaluation narrative presented in an objective and balanced manner and supportive of the risk characterization? If not, please provide some specific recommendations to improve the draft risk evaluation in this area.

Charge Question 6.3: Is the quality of the data used in the risk characterization appropriate for the purposes of the evaluation? If not, please provide specific examples and recommendations that may include additional data that EPA could consider in their assessment. **Charge Question 6.4:** Are the uncertainties and assumptions underlying the risk assessment transparently documented? If not, which uncertainties and assumptions could benefit from additional contextualization and/or clarification? **Charge Question 6.5:** What additional analyses might provide useful insight into the sensitivity of the risk characterization conclusions, including but not limited to the assumptions mentioned in Sections 2, 3, 4, and 5 of the draft risk evaluation?		
#	**Summary of Comments for Specific Issues Related to Charge Question 6**	**EPA/OPPT Response**
Clarity and completeness of review		
SACC	**SACC COMMENTS:** Table E-1 does not list ALL facilities reported CCl4 releases, only the 21 facilities with largest releases. A histogram (or estimated probability distribution curve) of annual releases from all 49 facilities would be useful in understanding the larger picture of releases.	A graphic has been added to Appendix E.
SACC	**SACC COMMENTS:** • Appendix F of the draft risk evaluation should include the specific information it is cited as having rather than referring the reader to U.S. EPA (2020), which appears to be incorrectly titled and dated. Appendix F is often inadequate when referencing important aspects of the exposure estimation. Recommendation: Expand Appendix F to include pertinent material from Supplemental Information on Occupational Exposure Assessment (U.S. EPA, 2020).	This appendix has been removed from final risk evaluation. The reader is referred to the supplemental file instead.
SACC	**SACC COMMENTS:** • A Committee member noted that Tables 4.3 to 4.6 of the draft risk evaluation are very helpful, although some Committee members preferred other formats versus stacked bars (*e.g.*, parallel bars). • A member commented that Figures 4-1 to 4-4 were very good, and that EPA should do the same type of	EPA appreciates this recommendation and will consider it for future risk evaluations

	graphical representation for dermal exposure.	
SACC	**SACC COMMENTS:** Recommendation: EPA should clearly describe which conditions of use pose unacceptable risks in the absence of PPE and further identify those conditions of use where assumed PPE use reduces risk to a level that the condition of use is assessed as having reasonable risks. This should be clarified in the Executive Summary (tables under Summary of Risk Determinations, p. 22-23) and in Table 4-13 and Table 5-1 of the draft risk evaluation.	EPA considers the uncertainties associated with each condition of use, and how the uncertainties may result in a risk estimate that overestimates or underestimates the risk. Based on such analysis, EPA determines whether or not the identified risks are unreasonable. Such consideration carries extra importance when the risk estimates are close to the benchmarks for acute, chronic non-cancer risks, and cancer risks. EPA's approach for developing exposure assessments for workers is to use reasonably available information and expert judgment. EPA considers each condition of use and uses exposure scenarios with and without PPE that may be applicable to particular worker tasks on a case-specific basis for a given chemical. For the purposes of determining whether or not a condition of use presents unreasonable risks, EPA incorporates assumptions regarding PPE use based on reasonably available information and professional judgment underlying the exposure scenarios. These assumptions are described in the unreasonable risk determination for each condition of use, in section 5.2. While EPA has evaluated worker risk with and without PPE, as a matter of policy, EPA does not believe it should assume that workers are unprotected by PPE where such PPE might be necessary to meet federal regulations, unless it has evidence that workers are unprotected. Additionally, in consideration of the uncertainties and variabilities in PPE usage, EPA uses the high-end exposure value when making its unreasonable risk determination in order to address those uncertainties. EPA has also outlined its PPE assumptions in section 5.1.
SACC	**SACC COMMENTS:** Recommendation: Consider incorporating additional	EPA is in the process of evaluating the body of reasonably available literature on AFs in order to determine whether to

	studies identified by the Committee as important into the risk evaluation. The following are some studies considered by the Committee to be important: • Environmental studies: Johnson et al. (2017); Kienzler et al. (2017). • Genotoxicity/toxicokinetics/mechanistic studies: Slater (1987); MAK (2000); Manibusan et al. (2007); Eastmond (2008); Hernandez et al. (2009); Borgert et al. (2015); Corthay (2014); Candeias and Gaipl (2016); Garner and Visser (2020); Sanzgiri et al. (1995 and 1997); Kim et al. (1990); Rao and Rechnagel (1968, 1969); Bruckner et al. (2002); Thrall et al. (2000); Kappus et al. (1985); WHO (1999); Seifert et al. (1994); Weber et al. (2003); Manibusan et al. (2007); Malaguarnera et al. (2012). • Spermatotoxicity studies: Smyth et al. (1936); Adams et al. (1952); El Faras et al. (2016); Turk et al. (2016). • Epidemiology studies: Hill et al. (2003); Heineman et al. (1994). • Studies on oxidative stress: Okora et al. (2019); Altinoz et al. (2018); Ritesh et al. (2015). It was noted that some of these studies listed above were initially identified, but not carried forward for evaluation and this is an example of how the TSCA systematic review system is not working as expected.	revise standards for application of AF and the acute to chronic ratio for the 20 high-priority substances undergoing TSCA risk evaluation. EPA will consider the (Kienzler, 2017) study in its assessment. Until the body of scientific evidence for AFs is evaluated, EPA will continue to use OPPT methodology as cited in the risk evaluation (U.S. EPA, 2013, 2012b) and apply an AF of 5 for acute and 10 for chronic fish and aquatic invertebrate data. EPA considers these AFs to be protective of fish and aquatic invertebrates from acute and chronic exposures to neutral organic substances such as carbon tetrachloride, which produce toxicity from narcosis. EPA does not have reasonably available information that carbon tetrachloride is a thyroid endocrine disruptor. EPA consulted (Johnson et al., 2017) while examining amphibian variation in sensitivity and constructing SSDs in the final risk assessment. EPA used the approach described in Section 1.5 of the final risk evaluation to evaluate, extract and integrate carbon tetrachloride's human health hazard and dose-response information from the identified studies. After implementation of this approach and methodology, EPA redesigned the weight of evidence (WOE) narrative for the identified human health hazards for carbon tetrachloride to improve clarity and transparency based on recommendations from SACC.
SACC	**SACC COMMENTS:** • One Committee member indicated that the word "benchmark" was used to represent two fundamentally different concepts in the draft risk evaluation, which both differ from how benchmark is typically used by EPA (U.S. EPA, 2012; Davis et al., 2011) and other organizations such as the European Food Safety	The use of the term benchmark has been clarified and harmonized with other TSCA risk evaluations. EPA will consider further clarifications and harmonization in future risk evaluations, as needed.

	Authority (EFSA, 2017; Haber et al., 2018) and may be a source of confusion. • For cancer effects, the draft risk evaluation defines benchmark risk as the target risk (10^{-4}) and BMD as the dose estimated to correspond to that target 10^{-4} risk. For noncancer effects, the benchmark MOE is a unitless factor that is divided into the POD (generally the NOAEL exposure) to determine a sufficiently safe exposure. Both uses differ from how EPA has used the BMD term previously, and also differ from the original purpose of the BMD. Recommendation: For cancer risk, the term BMD should be reserved for PODs that are estimated by BMDs corresponding to risks (benchmark responses [BMRs]) at the lower end of the observable range (*e.g.*, 0.1%), estimated using the methods discussed in U.S. EPA (2012). For noncancer risk, the "benchmark MOE" should be appropriately termed instead of the "total uncertainty factor (UF_T)."	
SACC	**SACC COMMENTS:** • Some Committee members found the explanation of the approach used to calculate HEDs using a pharmacokinetic model difficult to follow. It is not always clear if the dose being discussed represents the dose applied to a rodent, or the HED. • For example, it was not clear on first reading that the $BMDL_{10}$ of 14.3 mg/m^3 (line 4103) refers to the HED. Recommendation: EPA should adopt a method for distinguishing exposures to rodents from HEDs and apply this distinction consistently.	The dose response section in the final risk determination provides better characterization of POD derivation.
SACC	**SACC COMMENTS:** • The Committee expects that many readers will likely focus on risk determination values under conditions	Because carbon tetrachloride is an intermediate and is mostly used at large facilities, EPA assumes the use of a respirator with an APF of 50 and gloves with a PF of 20. The risk

	with and without PPE use, and not also carefully consider the background information about PPE presented in this draft risk evaluation. The risk evaluation should alert readers to pay attention to this information, and in particular, alert readers to conditions of use where the decision of no unreasonable risk is directly tied to assumptions of PPE use. • Whenever EPA derives or cites a risk that is not unreasonable because of the assumption of PPE use, a modifying phrase should be added to enhance attention to the limitations in this assumption (*e.g.*, EPA has determined that Condition of Use_x (Scenario_x) does not present an unreasonable risk contingent upon adherence to OSHA standards on exposure controls and PPE requirements and recommendations). Recommendation: Highlight for readers those conditions of use where the determination of no unreasonable risk is directly related to the assumption of PPE use.	evaluation also presents estimated risk in the absence of PPE and does not assume that ONUs use PPE. EPA must evaluate the conditions of use it expects to consider under TSCA in the risk evaluation and propose risk management for any condition of use which the Agency determines presents unreasonable risk. Risk management activities will only occur after EPA has completed the risk evaluation. See the Executive Summary, updated Risk Characterization (Section 4), and updated Risk Determination (Section 5) for more clarification on how these sections support each other and how new information submitted to or obtained by EPA following publication of the draft risk evaluation was incorporated.
SACC	**SACC COMMENTS:** • In Section 1.3, Regulatory and Assessment History (pp. 26-28), the draft risk evaluation mentions national and international laws to which CCl4 is subject (Subsection 1.3.1, p. 21, and Appendix A) and prior assessments by other national and international agencies with regulatory mandates on CCl4 (Table 1-3, p. 27). However, the section is not very informative. It needs to provide a brief and specific description of the relevance to the current risk evaluation, or whether the prior assessments have indeed addressed exposures and risks that EPA decided not to address in this risk evaluation (for example, risks to populations in close vicinity to major point sources). Having a statutory	Clarifying language about what pathways are under the jurisdiction of other EPA-administered statutes has been added to Section 1.4.3 of the Risk Evaluation.

	mandate for evaluating environmental or human health risk from a compound was not sufficient to demonstrate that indeed such evaluation has been done for all relevant situations. Recommendation: Provide more specific information about relevance of other legislation and the specifics of environmental or human health risk addressed by other organizations.	
SACC	**SACC COMMENTS:** • The production and releases of CCl4 are difficult to reconcile in terms of mass balance when comparing the releases reported in Table_Apx D-1 (Appendix D, p. 237; 2018 TRI Data) and the production volume listed in Table 1-2 (p. 26) for the CDR 2012 to 2015. In particular, the footer in Table 1-2 [*i.e.*, "The CDR data for the 2016 reporting period is available via ChemView…"] raises the question of why it was not added to the release volumes. Recommendation: Add explanatory information in Tables 1-2 and D-1 describing the differences between the reporting periods for production and release.	EPA noted in Table D-1 that carbon tetrachloride release data reported by facilities to TRI in 2017 was reviewed and available in 2018. Table 1-2 and Table_Apx D-1 are presenting the most recently available data. CDR data is collected every four years and includes data from the previous four years. CDR data is named for the year it is reported. Therefore, Table 1-2 presents production volumes from the 2016 CDR reporting period which includes data from 2012-2015. The 2020 CDR reporting period is in-progress (and will include data from 2016 to 2019) with the reporting period ending on November 30, 2020. CDR is a collection of basic exposure-related information on the types, quantities, and uses of chemical substances manufactured domestically or imported into the United States. The CDR rule, promulgated under the authority of Section 8(a) of TSCA, requires chemical substance manufacturers (including importers) to report manufacturing and processing data and industrial, commercial, and consumer use information for certain chemical substances on the TSCA Inventory. Meanwhile, TRI tracks the management of certain toxic

		chemicals that may pose a threat to human health and the environment. U.S. facilities in different industry sectors must report annually how much of each chemical is released to the environment and/or managed through recycling, energy recovery and treatment. Under the TRI rule, regulated facilities must report information on releases and other waste management for specific chemical substances in accordance with Section 313 of the Emergency Planning and Community Right-to-Know Act (EPCRA). TRI data is collected annually for the previous year and is named after the year of data it represents (not the reporting year). 2018 TRI data was collected in 2019 and 2019 data will not be published until January 2021.
SACC	**SACC COMMENTS:** A Committee member considers the following statement (p. 20, lines 737-739) to not be exactly true: "In each risk evaluation under TSCA section 6(b), EPA determines whether a chemical substance presents an unreasonable risk of injury to health or the environment, under the conditions of use. The determination does not consider costs or other non-risk factors." Decisions to set the target cancer risk for exposed workers at 10^{-4}, set MOE levels at 10 or 100, set BMR levels at 5% or 10%, set expected working life length, or apply UFs are all policy decisions that can involve costs or other non-risk factors. EPA should modify this statement.	EPA applied risk assessment methods tailored to the requirements of TSCA. TSCA compels EPA to conduct risk evaluations to determine whether a chemical substance presents unreasonable risk, without consideration of cost or other non-risk factors, under the conditions of use. EPA's decision to use a 10^{-4} cancer risk benchmark, specific MOEs and BMRs, and applied UFs are risk factors; the Agency does not consider these to be non-risk factors. In addition to assessing the cancer risk using a linear extrapolation approach and comparing the results to the standard cancer benchmark of $1x10^{-4}$, EPA also assessed cancer risk using a threshold approach. Based on the threshold approach, EPA identified MOEs for cancer risks. EPA used both the risk estimates derived from the linear extrapolation approach and the MOEs derived from the threshold approach for the unreasonable risk determinations for individuals exposed to carbon tetrachloride.

SACC	**SACC COMMENTS:** Terminology such as "slope" and "MS-combo model" are not referred or referenced and are applied in the draft risk evaluation under the assumption that other people are familiar with them.	A description of the MS-combo model has been added to the final risk evaluation.
SACC	**SACC COMMENTS:** • The draft risk evaluation (p. 28, line 1012) indicates that "EPA conducted public outreach and literature searches to collect information about carbon tetrachloride conditions of use…" without providing any specifics. Recommendation: Quantify what is entailed in the phrase "Public outreach and literature searches."	EPA conducted literature searches for reasonably available information and convened meetings with companies, industry groups, chemical users and other stakeholders to aid in identifying conditions of use and verifying conditions of use for carbon tetrachloride. All public outreach is available in the docket (EPA-HQ-OPPT-2016-0733). All cited references are available for public review, subject to limitations under TSCA section 14.
SACC	**SACC COMMENTS:** • EPA should look at how small changes in grouping conditions of use affect the conclusions. Consider parametrizing some of the qualitative assumptions or input different assumptions and assess how the risk conclusions vary. Recommendation: Consider performing a more robust sensitivity analysis such as the one proposed in Thabane et al. (2013) study.	EPA will consider this SACC recommendation in future risk evaluations.
SACC	**SACC COMMENTS:** The risk evaluation should reference environmental discharges and pathways that were addressed by other regulations by including hyperlinks that would direct the reader to the relevant regulations and documentation.	Clarifying language about what pathways are under other statutes has been added to Section 1.4.3 of the Risk Evaluation.
SACC	**SACC COMMENTS:** • Some key information is not located in the body of the draft risk evaluation, but the reader is referred to an appendix for detail. Once in the appendix, the reader is referred to a supplemental document for the	EPA reconsidered the appropriate placement of information in the final risk evaluation and made necessary changes to improve the exposure, hazard, and risk discussions in the body of the risk evaluation.

	information. This daisy chain of referrals complicates reading and comprehension. • The Committee encouraged placing the information and discussion that is crucial to establishing the exposure, hazard, and risk findings in the body of the risk evaluation, and placing the detailed arguments and computations in appendices or supplemental documents. Creating a concise and comprehensive discussion in the body of the risk evaluation is difficult but important to constituent understanding. Recommendation: Consider carefully which information needs to be provided explicitly in the body of the risk evaluation from the more detailed information available in the appendices.	
SACC	**SACC COMMENTS:** Recommendation: Consider reordering the presentation of materials in the draft risk evaluation to discuss environmental exposures, hazard, and risk characterization (Environment; new Section 2) before human health exposures, hazard, and risk characterization (Human Health; new Section 3) and followed by PESS exposures, hazard, and risk characterization (PESS; new Section 4). • A majority of the Committee supported this recommendation as a way to reduce repetition that occurs throughout the document and improve clarity and readability. • The remaining Committee members proposed presenting the environmental and occupational exposure, hazard, and risk characterizations as two distinct sections instead of rotating through these topics in Section 2 (Exposures), Section 3 (Hazards), and Section 4 (Risk Characterization).	This is a cross-cutting issue raised on the processes that EPA is going to be looking at in a more holistic way for the next 20 TSCA risk evaluations and will not be addressed in the carbon tetrachloride risk evaluation.
SACC	**SACC COMMENTS:**	This is a cross-cutting issue raised on the processes that EPA

	Recommendation: Optimize the use of active links within the risk evaluation and provide external access to increase readability and transparency. • It would be very helpful to improving reading comprehension if links could be provided that tie directly to the subsection (*e.g.*, the specific table, section, page) of the document (*e.g.*, appendix or supplemental document) where the specific information is located. Currently, links are to a whole document that require readers to search the document for the specific information referenced. Specifically, key values in summary tables (*e.g.*, tables of exposure estimates, PODs, risk estimates) should be linked either internally to where they are discussed in the risk evaluation document or externally to documents where the value is derived and/or discussed.	is going to be looking at in a more holistic way for the next 20 TSCA risk evaluations. Additional linking has been added in the carbon tetrachloride risk evaluation.
SACC	**SACC COMMENTS:** The Committee noted that the names of EPA staff who were involved in writing the current document are not listed. The Committee hopes that that these staff members will be recognized in the immediate future for their work.	Names of staff have been added.
33	**PUBLIC COMMENTS:** The TSCA program should list the individual cancer sites – including brain and nervous system cancers for CCl4 – as is done by the EPA IRIS program and IARC. This information is important for researchers wanting to conduct risk studies, employers wanting to inform and protect vulnerable workers, insurers wanting to identify liability, workplace compensation programs wanting to identify causality, and others.	EPA lists the individual cancer sites in the table of epidemiologic literature on cancers.
45	**PUBLIC COMMENTS:** The dose-response section (3.2.5) and the accompanying supplemental BMD modeling document are poorly	The information on the dose-response section has been expanded in the final risk evaluation.

	described. It has been customary in other risk evaluations to provide summary tables listing all of the various model combinations, with the final selected data set highlighted. Additional summaries linking the BMD modeling results to the POD selection process should be provided. This would provide additional clarity to the POD discussion section.	
45	**PUBLIC COMMENTS:** EPA should provide more discussion in these risk evaluations about the substance of its intra-agency coordination with program offices about existing regulatory requirements that protect various media pathways (*i.e.*, air, water, land).	Clarifying language about what pathways are under the jurisdiction of other EPA-administered statutes has been added to Section 1.4.3 of the Risk Evaluation. Discussions across EPA's program offices occur as the risk evaluation is conducted and refined. Communication and coordination between program offices within EPA occurs regularly on TSCA-related efforts.
Objective presentation of risk findings		
26	**PUBLIC COMMENTS:** EPA's exclusion of CCl4's use in the aerospace industry is based on an unsubstantiated personal communication, which the public cannot access to assess its accuracy and reliability. EPA cannot rely on unverified and potentially unrepresentative personal communications. EPA should exercise its authority under TSCA section 8 to obtain information that could be used to confirm or negate this personal communication.	EPA's exclusion of aerospace uses from the conditions of use for carbon tetrachloride is based on communication with Aerospace Industries Association (AIA) quoted in the risk evaluation. Specific details on this communication are described in section 1.4.3.1. As described in this section, AIA explained that uses previously identified as conditions of use have been discontinued and EPA determined that the uses are not intended, known, or reasonably foreseen to occur. As a result, EPA did not include these uses in the risk evaluation.
Appropriateness and quality of data used in risk evaluation		
SACC	**SACC COMMENTS:** • The article selection for a systematic review should follow established guidelines, such as Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for observational studies. All epidemiologic journals currently require a PRISMA	The major components of a PRISMA diagram (*i.e.*, identification, screening, and eligibility of final included articles) are represented in the *Literature Flow Diagram for Human Health Hazard Data Sources*. Literature Flow Diagrams were developed as an overview of the systematic review process and (see Figures 1.5-1.9). Literature Flow

	figure that shows the data identification, screening, and eligibility of final included articles. The SACC report includes an example PRISMA 2009 Flow Diagram. • In addition, the exclusion and inclusion criteria should be defined *a priori* and applied to the article selection and identification. This approach has been in place for over 10 years and should be adopted for TSCA evaluations for assessing epidemiologic studies. • This is one solution to the issue with understanding the process for selecting and excluding articles and related justifications that the Committee has discussed in previous reviews. Recommendation: Modify epidemiologic study identification and selection methodology to comply with established PRISMA guidelines.	Diagrams in Section 1.5.1 of the risk evaluation. EPA developed inclusion and exclusion criteria for epidemiologic studies *a priori* and applied these criteria during the screening phase of the systematic review. See the *Strategy for Conducting Literature Searches for Carbon Tetrachloride (CCL4): Supplemental Document to the TSCA Scope Document* for the initial inclusion/exclusion screening criteria applied during the title/abstract screening for relevancy phase of the systematic review process for perc (see Section 4).The *Problem Formulation of the Risk Evaluation for Carbon Tetrachloride* has the chemical-specific inclusion/exclusion criteria applied during the full-text screening phase of the systematic review process (see Appendix F).
SACC	**SACC COMMENTS:** • The Committee suggests using one of the many published, validated systems for evaluation of the quality of the literature, such as the National Institutes of Health (NIH) assessment tool (NIH Study Quality Assessment Tools), or others available in the literature. This approach would allow for a non-biased, standardized, accepted evaluation, comparable to other evaluations. In addition, evaluation is usually performed by two independent reviewers, and any discrepancy in findings are discussed and consensus is reached. Recommendation: Use current best practice methods for quality review of literature including use of two independent reviewers.	EPA/OPPT's quality evaluation method was developed following identification and review of various published qualitative and quantitative scoring systems when developing the systematic review process for the first 10 TSCA risk evaluations (*e.g.*, OHAT Risk of Bias tool, CRED, etc.; see Appendix A of the *Application of Systematic Review in TSCA Risk Evaluations* document and references therein), as well as soliciting input from scientists based on their expert knowledge about evaluating various data/information sources specifically for risk assessment purposes. The NASEM TSCA Committee will review EPA's systematic review process and provide recommendations for improvement. EPA will consider future revisions to the TSCA data quality evaluation tools after that time.
SACC	**SACC COMMENTS:** • One Committee member submitted a relatively simple, standard template for data extraction from	The NASEM TSCA Committee will review EPA's systematic review process, and EPA will consider revisions to the process based on their recommendations.

	epidemiology studies. When using this template, the specifics of data extraction must be decided before evaluating the study. The template also included objective criteria for quality evaluation of studies, so both the criteria for quality scoring and data extraction are decided before looking at the findings. Recommendation: Continue to improve the systematic review process.	
43, 23, 41, 30	**PUBLIC COMMENTS:** • The TSCA method represents a deeply flawed and unscientific approach to systematic review and will compromise the quality, validity, and protectiveness of EPA's risk evaluations (*e.g.*, see commentary published in the American Journal of Public Health). The method lacks transparency and is not empirically based, making it likely to have resulted in a biased evidence base. • EPA should address the SACC's prior comments on the TSCA method and incorporate the recommended changes. • The TSCA method departs radically from accepted scientific principles for systematic review adopted by the IOM NTP, and EPA's IRIS program and endorsed by the NAS and other peer review bodies. • EPA should not use the TSCA systematic review method until it is validated by the NAS. The review by NAS is not likely to be completed before the risk evaluations for the first 10 chemicals have gone through a round of public comment and peer review. • In completing the ongoing risk evaluations, EPA must adopt a well-established systematic review method, such as those developed by IOM, NTP (Office of Health Assessment and Translation [OHAT]), EPA's	EPA published the title/abstract inclusion/exclusion criteria for carbon tetrachloride in Appendix E of the *Strategy for Conducting Literature Searches for Carbon Tetrachloride* and inclusion/exclusion criteria statements used during full text screening in Appendix F to the *Problem Formulation of the Risk Evaluation for Carbon Tetrachloride*. Data quality criteria used for scoring each discipline are provided in a separate document titled *Application of Systematic Review in TSCA Risk Evaluations,* which also outlines evidence integration strategies that will be further developed for the next risk evaluations. EPA consulted multiple systematic review frameworks and the IRIS program when developing the systematic review process. EPA is reviewing its data quality criteria and will publish a protocol document for the next TSCA risk evaluations. To date, EPA has already made changes to the physical chemical, environmental, epidemiological criteria since the *Application of Systematic Review in TSCA Risk Evaluations* was published. These changes included validation and improvement efforts to ensure that the most relevant studies were included in the TSCA risk evaluations. The most up-to-date data quality evaluation criteria will be available for

	IRIS program, or the University of California, San Francisco (Navigation Guide), that is endorsed by the NAS and other peer reviewers.	review in the upcoming the *Systematic Review Protocol Supporting the TSCA Risk Evaluations* document (under development). EPA anticipates feedback from the NASEM TSCA Committee on its systematic review process, including the epidemiological data quality criteria and will carefully review and implement relevant recommendations.
43	**PUBLIC COMMENTS:** The TSCA approach applies a rigid scoring system to grade the "quality" of studies. This system could result in many studies being arbitrarily classified as "poor" or "unacceptable" based on a small number of reporting or methodology limitations that do not negate their overall value. Other systematic review methodologies do not use numerical scoring systems for assessing study quality and the NAS recommends strongly against such scoring. The SACC previously noted that "The Agency should provide justification for using a weighted scoring system and the rationale for the specific metrics used for differential weighting in its evaluation of studies."	Appendix A of the *Application of Systematic Review in TSCA Risk Evaluations* explains the basis for EPA/OPPT's development of a numerical scoring system to inform the characterization of the data/information sources during the data integration phase. The goal is to provide transparency and consistency to the evaluation process along with creating evaluation strategies that meet the TSCA science standards for various data/information streams. EPA/OPPT's quality evaluation method was developed following identification and review of various published qualitative and quantitative scoring systems to inform our own fit-for-purpose tool. The development process involved reviewing various evaluation tools/frameworks (*e.g.*, OHAT Risk of Bias tool, CRED, *etc.*; see Table 1 and Appendix A of the TSCA SR document and references therein), as well as soliciting input from scientists based on their expert knowledge about evaluating various data/information sources for risk assessment purposes. While there are many published systematic review tools available for human health and environmental health hazard assessment, no systematic review tools were identified that encompass either exposure assessment (*e.g.* general population exposures, occupational exposures and industrial releases) or fate and transport assessment.

		In order to ascertain the quality of the reasonably available data, EPA used a numerical scoring system to assign a qualitative rating. This approach added consistency and transparency to the evaluation process. Scores were used for the purpose of assigning the confidence level rating of High, Medium, Low, or Unacceptable, and inform the characterization of data/information sources during the data integration phase. In all evaluation strategies, professional judgment was employed to determine the adequacy or appropriateness of the qualitative rating assigned by the numerical scoring system.
41, 43	**PUBLIC COMMENTS:** • EPA fails to use a protocol that outlines the pre-established methods to be used throughout the systematic review process. This directly contradicts the EPA's 2017 framework rules mandating that the Agency use "a pre-established protocol" to conduct risk assessments. A protocol for the review needs to be established in advance of individual evaluations to eliminate the potential for bias and to assure that evidence reviews are conducted using consistent, well-defined criteria. • EPA must immediately implement protocols for all future draft risk evaluations. The use of pre-established protocols minimizes biases in the evidence base by explicitly pre-defining how questions will be formulated, searches will be conducted, eligibility criteria will be applied, and quality of the included studies will be assessed. It allows greater transparency in the decision-making process throughout the systematic review and is a fundamental element required to ensure the integrity of evidence-based	EPA's *Application of Systematic Review in TSCA Risk Evaluations* document and several supplemental documents demonstrate how systematic review was conducted for the first 10 chemicals undergoing risk evaluation under TSCA. As described in the *Application of Systematic Review in TSCA Risk Evaluations*, EPA/OPPT implemented a structured process of identifying, evaluating and integrating evidence for both the hazard and exposure assessments developed during the TSCA risk evaluation process. Because EPA/OPPT developed and implemented systematic review processes and procedures in tandem with development of actual TSCA risk evaluations, EPA/OPPT acknowledged it expected that new approaches and/or methods would be developed to address specific assessment needs for the relatively large and diverse chemical space under TSCA. Thus, EPA/OPPT expected to document the progress of implementing systematic review in the draft risk evaluations and through publication of supplemental documents.

	evaluations.	The TSCA systematic review process is undergoing improvements for the next risk evaluations and includes updates to better align with the systematic review best practices that commenters indicated in the public comments. EPA may need to develop new methods and approaches to ensure that the systematic review process is sensitive to the constraints and requirements applicable to risk evaluations under TSCA including tight statutory deadlines. The body of information compiled in the data quality and data extraction supplemental files accompanying each TSCA Risk Evaluation are the primary pool of studies that were considered for the first 10 risk evaluations. In addition, other data sources and information will be considered and possibly incorporated in the draft risk evaluations based on information submitted during public comment periods, peer review comments and targeted supplemental searches (*e.g.*, to locate specific data for building exposure scenarios and modeling). EPA is continuously creating and improving methods for efficiently evaluating the overall body of evidence and numerous changes in the methods were due to validation and improvement efforts to ensure that the most relevant studies were included in the TSCA risk evaluations. The most up-to-date data quality evaluation criteria will be available for review in the upcoming the *Systematic Review Protocol Supporting the TSCA Risk Evaluations* document (under development)
41, 43	**PUBLIC COMMENTS:** • EPA fails to use pre-established methods for evidence integration. The TSCA approach fails to address critical elements, including identification and evaluation of each stream of evidence and integration	When synthesizing and integrating evidence for each human health hazard endpoint, EPA considered quality, consistency, relevancy, coherence and biological plausibility as specified in *Application of Systematic Review in TSCA Risk Evaluations.* EPA used an informal framework for most

	of evidence as necessary and appropriate based on strengths, limitations, and relevance. The draft risk evaluation fails to clearly define how the quality of the body of evidence has been evaluated for each evidence stream and it has failed to pre-specify the method for integrating two or more streams of evidence in formulating the final conclusions. • EPA should use an approach to evidence integration that has been recommended and successfully applied by the IARC, NTP's OHAT, the Navigation Guide, or the NAS. • The data integration process should consist of: assigning an overall rating in the confidence of the body of evidence for each specified outcome using explicit, predefined criteria; translating the overall rating into a conclusion on the level of evidence for a health effect; and then formulating a hazard identification conclusion. Human and animal evidence, when available, should be integrated, while mechanistic data may be used to help inform the final conclusions.	endpoints but did array the immunological evidence within a more formal framework to respond to a comment by the SACC (see Appendix A below and Appendix M in the risk evaluation). Sections 3.2.3 and 3.3.4 describe EPA's process of weighing and integrating scientific evidence for hazard endpoints. EPA is developing and implementing more formal and structured data integration strategies for the next set of TSCA chemical risk evaluations. In addition, EPA anticipates feedback from the NASEM TSCA Committee on its systematic review process and will carefully review and implement relevant recommendations.
41, 43	**PUBLIC COMMENTS:** • EPA continues to use methods that lack transparency to identify "key/supporting/influential information," and does not provide the details of the methods for the "hierarchy of preferences" approach that excludes relevant studies. The "hierarchy of preferences" is a new concept that was not part of the original TSCA systematic review method document, nor in the scoping or problem formulation documents, and has not been subject to peer review or public comment. • EPA does not explain why some types of studies should receive preference over others. There are no	Different lines of evidence are routinely used in TSCA chemical assessments because of data availability, sources, underlying documentation, and quality varies. EPA preferentially relies on a variety of test and analog data. In the absence of suitable test data, predictive modeling tools may be used. For environmental hazards, if the modeling tools cannot provide predictions to an endpoint of interest, then calculations like acute-to-chronic ratios can be used to fill in data gaps. PECO/RESO statements or a modified framework were used to describe the full-text inclusion and exclusion criteria for

	objective criteria for determining which evidence to rely on and which to exclude, undermining transparency and consistency and encouraging subjective judgments. There is a lack of clarity on how EPA chose and evaluated the key sources, which at their time of incorporation, outweigh the results from EPA's screening process. There is also a lack of clarity on how EPA came to its decisions about which studies it chose to exclude and which to include in its supplemental information. This pattern obscures the evidence base for this draft risk evaluation, potentially leading to biased results.	selecting relevant references. These criteria are provided in the TSCA Problem Formulation documents for each chemical as some criteria reflect chemical-specific issues that are better discussed in each chemical risk evaluation.
41, 43	**PUBLIC COMMENTS:** • The updated TSCA data quality criteria for epidemiological studies make it more difficult for epidemiological studies to be scored as high quality and thus limit the weight that they receive in TSCA risk evaluations. The method can exclude a study based on only one "unacceptable" criterion rather than considering all relevant science while accounting for "strengths and limitations" as required by TSCA. EPA has failed to explain or justify the updated criteria. • The criteria are based on an arbitrary list of metrics including several scoring metrics not related to bias, but rather to reporting. In Metric 13 'Statistical power,' a study can only be scored as 'Medium' or 'Unacceptable.' In fact, with EPA's updated criteria, epidemiological studies can no longer score high on seven metrics, but no such change has been made for the animal or *in vitro* studies. Further, there is no empirical justification for these 'scores' on the different metrics.	The epidemiologic criteria were revised to more stringently distinguish between High, Medium and Low studies (see revisions in the supplemental file to the carbon tetrachloride: Updates to the Data Quality Criteria for Epidemiological Studies). After additional piloting of the criteria, EPA found that the initial iteration of the epidemiological data quality criteria (as published in the *Application of Systematic Review in TSCA Risk Evaluations*) was inadvertently skewing quality scores toward the tail ends of the scoring spectrum (High and Unacceptable). In order for the criteria to represent a more accurate depiction of the quality levels of the epi literature, the criteria were revised using two methods. The first method was to make the unacceptable metrics less stringent. This was accomplished by either rewording the metrics to allow for more professional judgment in the interpretation of the unacceptable criterion, or in some cases, completely removing the unacceptable bin from metrics that EPA determined were not influential enough to completely disqualify a study from consideration (mostly metrics in the Analysis and Biomonitoring domain). EPA found that these

		criteria changes greatly reduced the type one error in the Unacceptable scoring. No acceptable studies were inaccurately classified as Unacceptable. The second method was to reduce the number of studies that received an overall High rating. The majority of overall scores in EPA's initial evaluations during piloting tended to be High. Therefore, EPA strived to revise the criteria to provide more degradation in the scoring to more accurately and objectively distinguish studies of the highest quality from medium and low-quality studies. To do this, EPA removed the High criterion from some metrics, particularly in dichotomous metrics (High/Low or High/Unacceptable) that were primarily being binned as High by reviewers across the majority of the studies. These dichotomous metrics were contributing to the overall quality scores being skewed towards High. To address this, EPA shifted some of the dichotomous metrics such that the highest metric score possible (for all studies) is a Medium. The change led to the dichotomous metrics having less significant impact to the numerical scoring and the overall quality rating for each study. With the aforementioned changes to the criteria, EPA observed fewer studies with Unacceptable ratings and more studies shifting from High to Medium, with only the highest quality studies receiving a High overall rating. Out of the ~200 relevant epidemiologic studies and cohorts evaluated for data quality for the first 10 TSCA chemicals, the majority (~80%) still scored as High or Medium. The remaining ~20% of studies scored Low or Unacceptable. EPA is confident that no studies of acceptable quality were inappropriately assigned as Unacceptable. EPA is also confident that the revised

		criteria bins the quality levels of these epi studies more appropriately than the previous iteration. Additional refinements to the epidemiologic data evaluation criteria are likely to occur as EPA's validation and process improvement efforts continue. EPA anticipates feedback from the NASEM TSCA Committee on its systematic review process, including the epidemiological data quality criteria, and will carefully review and implement relevant recommendations.
41	**PUBLIC COMMENTS:** EPA fails to transparently apply predefined eligibility criteria to the references in the literature search. The Populations, Exposures, Comparators, and Outcomes (PECO) statement (framework) should shape the entire review process, including the search strategy to be used, the study eligibility criteria to be applied, how the data will be extracted from the included studies, the strategy for synthesizing the evidence, and how the results will be reported. The PECO statement should be designed to "minimize the risk of researcher biases influencing the ultimate results of the SR."	EPA/OPPT developed and applied inclusion and exclusion criteria during title/abstract and full text screening to identify information potentially relevant for the risk evaluation process. This step also classifies the references into useful categories (*e.g.*, *on-topic* versus *off-topic*, human versus animal hazard) to facilitate the sorting of information through the systematic review process. The results of initial title/abstract screening for each of the first 10 chemical risk evaluations are available in an EPA page for Chemicals Undergoing Risk Evaluation under TSCA. A summary of the Full Text Screening conducted for the first 10 TSCA risk evaluations is described in Section 3.2.2.2.1 of the draft risk evaluation and summarized here. The full text screening was conducted while EPA/OPPT refined the scope of the TSCA risk evaluations and developed the problem formulation documents for the first 10 chemical substances. PECO statements or a modified framework were used to describe the full-text inclusion and exclusion criteria for selecting relevant references. These criteria are provided in

		the TSCA Problem Formulation documents for each chemical as some criteria reflect chemical-specific issues that are better discussed in each chemical assessment. Each article was generally screened by two independent reviewers using specialized web-based software (*i.e.*, DistillerSR)[1]. Screeners were assigned batches of references after conducing pilot testing. Screening forms facilitated the reference review process by asking a series of questions based on pre-determined eligibility criteria. DistillerSR was used to manage the workflow of the screening process and document the eligibility decisions for each reference. The screeners resolved conflicts by consensus, or consultation with an independent individual(s). As indicated in section 3.2.2.1 of the TSCA SR document, EPA/OPPT used the infrastructure of the ECOTOX knowledgebase (U.S. EPA, 2018a) to identify single chemical toxicity data for aquatic life and terrestrial life. It uses a comprehensive chemical-specific literature search of the open literature that is conducted according to Standard Operating Procedures (SOPs), including specific SOPs to fit the needs of the TSCA risk evaluations[2]. Due to its well-established methods to gather high quality data, ECOTOX processes and data are widely accepted and used by a variety of domestic and international organizations and researchers. The ECOTOX literature search strategy is documented in the *Strategy for Conducting Literature Searches* documents for each of the ten TSCA risk evaluations and the data screening and extraction protocols are described ECOTOX SOPs[3]. [1] In addition to using DistillerSR, EPA/OPPT is exploring automation and machine learning tools for data screening and prioritization activities (*e.g.*, SWIFT-Review, SWIFT-Active Screener, Dragon, DoCTER).

		SWIFT is an acronym for "Sciome Workbench for Interactive Computer-Facilitated Text-mining". [2] The ECOTOX SOPs can be found at https://cfpub.epa.gov/ecotox/help.cfm?helptabs=tab4. [3] The ECOTOX SOPs for TSCA work can be found at https://cfpub.epa.gov/ecotox/blackbox/help/OPPTRADCodingGuidelinesSOP.pdf and https://cfpub.epa.gov/ecotox/blackbox/help/OPPTRADReportsSOP.pdf.
41	**PUBLIC COMMENTS:** • EPA does not provide a method for how to determine the "adequacy" of the statistical power of a study and fails to provide any rationale for excluding studies with <80% statistical power. In Metric 13 'Statistical power' of the epidemiological criteria, EPA has confused bias with imprecision, as individual primary studies that are "underpowered" are still valuable to decision-making. Small studies may be imprecise, but that does not mean they should be confused with a study that is biased. • Importantly, when combined in a meta-analysis that increases the statistical power of the body of evidence, small studies that are underpowered can demonstrate an effect between an exposure and health outcomes. For example, in a 2017 systematic review by Lam et al. entitled "Developmental PBDE Exposure and IQ/ADHD in Childhood: A Systematic Review and Meta-analysis," none of the four high-quality studies included in the meta-analysis reported a power calculation, and therefore would have been considered 'unacceptable' by EPA.	EPA acknowledges that this metric needs further refinement and agrees that poorly powered studies can still be useful when combined in meta-analysis. Additional refinements to the epidemiologic data evaluation criteria are likely to occur as EPA's validation and process improvement efforts continue. EPA has requested feedback from the NASEM TSCA Committee on its systematic review process, including the epidemiological data quality criteria, and will carefully review and implement relevant recommendations.
41	**PUBLIC COMMENTS:** Rather than exclude a study based on a lack of reporting, EPA should instead attempt to request the missing information required to make the determination from the	The TSCA evaluation strategies consider methodological design and implementation and reporting within the existing domains and metrics. Since it is difficult to have high confidence in data where the underlying methods are

	study authors. If EPA is not able to retrieve this missing information from the study authors, a potential bias (if the metric being assessed relates to bias and not reporting) may then be considered in the study. However, the study should not be excluded from the body of evidence due to this one criterion.	unreported or poorly reported, EPA assesses reporting and methodological quality simultaneously. However, EPA recognizes the challenge of discerning between a deficit in reporting and a problem in the underlying methodological quality of the data/information source. Developing a reporting checklist, guidance document or a separate reporting quality domain may be possible in the future as EPA uses and optimizes the evaluation strategies. EPA also designed evaluation criteria that consider risk of bias and Bradford Hill aspects when assessing the quality of animal toxicity and epidemiological studies. Refer to Appendices F, G and H of the *Application of Systematic Review in TSCA Risk Evaluations* document for more information.
SACC	**SACC COMMENTS:** • EPA relies heavily on prior CCl4 assessments done by other agencies. There is a potential for missing key or supporting studies if prior assessments did not adhere to systematic review. The risk evaluation should include clear statements as to whether principles of systematic review were applied in the prior assessments and, if so, to what extents. • There is still an issue of insufficient transparency in the application of systematic review for selecting data sources and references used in support of the risk evaluation and risk characterization. • One Committee member proposed to develop a "key" to the reference section of the risk evaluation to make it easy to identify key and supporting sources, identify the section of the evaluation where they are pertinent, know whether the citations were subject to data quality evaluation (including, if applicable, the specific prior review in which it was included), and identify sources that were not subject to data quality evaluation and the	This is a cross-cutting issue raised on the processes and the science and methods that EPA is going to be looking at in a more holistic way for the next 20 TSCA risk evaluations. All data used in the carbon tetrachloride risk evaluation were evaluated under the TSCA systematic review process.

	reason why. Recommendation: Develop and display a "key" for the reference section that facilitates identifying and tracing sources throughout the process of systematic peer review and data source evaluation/validation.	
SACC	**SACC COMMENTS:** The quality of several studies was described as unacceptable but they were used in the risk evaluation, nonetheless. This appears to undermine the goal of using the best quality studies. An alternative descriptor such as "poor" could be used to differentiate these studies from those that are completely unacceptable. The term "unacceptable" should be restricted to a study deemed of unacceptable quality for a reason (*i.e.*, unacceptable for...). The systematic review needs to provide the context for which a publication may be acceptable or not. This context is not always clear because the names assigned to criteria for selection in the systematic review process do not always reflect clearly the criteria.	Unacceptable dermal studies are no longer used in the derivation of PODs, an alternate approach is used instead.
31	**PUBLIC COMMENTS:** EPA did not complete a data quality review of every cited genotoxicity study. The supplemental review file for human health hazard studies only includes four *in vitro* studies. Yet, Appendix I summarizes a number of other studies (excerpted from the EPA IRIS assessment) that do not appear to have undergone a data quality review according to the TSCA systematic review protocol.	Data quality review for every cited genotoxicity study is presented in final risk evaluation.
41	**PUBLIC COMMENTS:** There is inconsistency in the reporting of the included studies in the draft risk evaluation and the accompanying supplementary files. In 'Carbon tetrachloride Bibliography: Supplemental File for the TSCA Scope Document,' there are 107 pages of "On Topic" references	A review of the *on topic* human health references after the title and abstract screening revealed a large number of animal studies that were likely to be of limited use for the following reasons: (1) The aim of the study was to induce a disease state in an animal (*e.g.*, cirrhosis, fibrosis, organ damage: liver, kidney, testes and others) rather than evaluate the effects of

	following title and abstract screening for human health hazard with approximately 2,782-2,996 references. However, in Figure 1-8 of the CCl4 draft risk evaluation, EPA states that: "The literature search strategy used to gather human health hazard information for carbon tetrachloride yielded 6,489 studies… Of the 6,489 studies identified for carbon tetrachloride 6,454 were excluded as off topic during the title and abstract screening phase." Therefore, according to EPA after title and abstract screening, there were only 35 "On Topic" studies included in the draft risk evaluation. This is inconsistent with the bibliography supplemental file for the TSCA Scope Document, which demonstrates there are >2,500 "On Topic" references following the title and abstract screening. EPA has not accounted for or screened these >2,500 references in the draft risk evaluation.	carbon tetrachloride exposure in animals and/or (2) Exposure was via injection. In order to refine the search results for full-text screening, the inclusion/exclusion criteria were revised to remove these studies from the "on topic" pool. Appendix B in the Problem Formulation describes the process used to re-screen the references identified as "on topic" in the first screening round, including prioritizing the literature for screening and the re-categorization criteria applied during the re-screening and tagging.
27, 41	**PUBLIC COMMENTS:** The draft risk assessment dismissed 99.45% of the 6,489 studies, found when searching for CCl4 hazards, at the "title/abstract screening" stage without any characterization. The criteria used to dismiss so many findings were not provided. Although EPA states that "Because systematic review is an iterative process, EPA/OPPT expects that some references may move from the on-topic to the off-topic category and vice versa," this does not justify the exclusion of 2,500-3,000 "On Topic" references for Human Health Hazards without explanation. The SACC should charge EPA to go back to the literature screening stage and apply the logic that there is no reason to dismiss a relevant toxicity finding, short of any obvious irrelevancy.	EPA published the title/abstract inclusion/exclusion criteria for carbon tetrachloride in Appendix E of the *Strategy for Conducting Literature Searches for Carbon Tetrachloride* and inclusion/exclusion criteria statements used during full text screening in an appendix to the problem formulation document for carbon tetrachloride. Data quality criteria used for scoring each discipline are provided in a separate document titled *Application of Systematic Review in TSCA Risk Evaluations,* which also outlines evidence integration strategies that will be further developed for the next risk evaluations.
41	**PUBLIC COMMENTS:**	A review of the *on topic* human health references after the title and abstract screening revealed a large number of animal

	The numbers shown in the flow diagram Figure 1-8 do not accurately reflect the numbers at each step and do not account for all of the 6,489 references identified from the 'Data Search Results.' As shown, in the 'Data Screening Step,' of the 6,471 studies, 6,454 studies were excluded. Therefore, 17 studies should have moved to the 'Data Evaluation Step,' not 15 as shown here, with 18 'Key/supporting data sources' being added, for a total of 35 studies entering the 'Data Evaluation,' not 33 as shown here.	studies that were likely to be of limited use for the following reasons: (1) The aim of the study was to induce a disease state in an animal (*e.g.*, cirrhosis, fibrosis, organ damage: liver, kidney, testes and others) rather than evaluate the effects of carbon tetrachloride exposure in animals and/or (2) Exposure was via injection. In order to refine the search results for full-text screening, the inclusion/exclusion criteria were revised to remove these studies from the "on topic" pool. Appendix B in the Problem Formulation describes the process used to re-screen the references identified as "on topic" in the first screening round, including prioritizing the literature for screening and the re-categorization criteria applied during the re-screening and tagging.
41	**PUBLIC COMMENTS:** In Figure 1-5, there are 150 data sources included at the 'Data Extraction/Data Evaluation Step' and 141 of these are excluded without any justification. Studies that make it to 'Full text screening' but are excluded thereafter should only be excluded with an explicit justification.	The sources used to collect data were all subjected to data quality evaluations based on metrics presented in the *Application of Systematic Review in TSCA Risk Evaluations* document, and the full data quality assessments are presented in a supplemental file.
41	**PUBLIC COMMENTS:** The way in which EPA developed and applied the eligibility criteria for references is deeply concerning. The literature and screening strategy is described in the Scope Document, which was published in June 2017. The results of the screening of literature search were published in 'Carbon tetrachloride (CASRN 56-23-5) Bibliography: Supplemental File for the TSCA Scope Document' (webpage 'last updated on June 22, 2017'). As highlighted in the draft risk evaluation, for studies determined to be 'on-topic' after title and abstract screening, EPA conducted full text screening to further exclude references that were not relevant to the risk evaluation. The inclusion and exclusion criteria for full text screening were published in	EPA designed evaluation criteria that consider risk of bias and Bradford Hill aspects when assessing the quality of animal toxicity and epidemiological studies. Refer to Appendices F, G and H of the *Application of Systematic Review in TSCA Risk Evaluations* document for more information. EPA is continuously creating and improving methods for efficiently evaluating the overall body of evidence and numerous changes in the methods were due to validation and improvement efforts to ensure that the most relevant studies were included in the TSCA risk evaluations. The most up-to-date data quality evaluation criteria will be available for review in the upcoming the *Systematic Review Protocol*

	the problem formulation for CCl4 (published in May 2018), after the searches and initial screening had been completed. The timing of this is very concerning as the PECO framework was developed after the studies had already been identified in the literature search and screened at the title and abstract stage and therefore could have been developed to include/exclude studies that would support a pre-defined health hazard conclusion. EPA's failure to predefine the study eligibility criteria, applied to the 'on topic' references in the draft risk evaluation, introduces significant researcher bias that most likely impacted the results of the draft risk evaluation.	*Supporting the TSCA Risk Evaluations* document (under development).
41	**PUBLIC COMMENTS:** In Figure 3-1 of the draft risk evaluation, EPA conflates data quality evaluation and evidence integration in the 'Human Health Hazard Assessment' and does not clearly outline how these two critically important steps were completed. In section 3.2.4, EPA describes how they conflate both an evaluation of the quality of the body of evidence and the evidence integration steps during the 'weight of the scientific evidence' process: "Factors considered in weighing the scientific evidence included consistency and coherence among human and animal studies, quality of the studies (such as whether studies exhibited design flaws that made them unacceptable) and biological plausibility." EPA does not rate the confidence in the body of evidence or follow a predefined evidence integration process that transparently demonstrates how it arrived at is its final conclusion. Therefore, it is unclear how EPA translated the available evidence into its final conclusion. EPA must immediately implement an evidence integration method that is consistent with best practice in	The sources used to collect human health data for carbon tetrachloride were all subjected to data quality evaluations based on metrics presented in the *Application of Systematic Review in TSCA Risk Evaluations* document, and the full data quality assessments are presented in a supplemental file. EPA is developing and implementing more formal and structured data integration strategies for the next set of TSCA chemical risk evaluations. In addition, EPA requested feedback from the NASEM TSCA Committee on its systematic review process and will carefully review and implement relevant recommendations.

	systematic review and transparently present how the conclusions were reached.	
41	**PUBLIC COMMENTS:** EPA's draft risk evaluation references Klimisch scores (or European Chemicals Agency [ECHA] reliability scores) when considering dermal and inhalation risks. These scores are invoked particularly when discussing studies in EPA's IRIS assessment for CCl4, but they are not present in the IRIS assessment and only seem to appear behind studies that score poorly. It is deeply concerning that EPA is invoking a potentially biased and non-empirically validated instrument when outlining dermal and inhalation risks from CCl4, as it may present issues with regard to internal validity and external generalizability.	Klimisch scores are not presented in final risk evaluation.
Editorial comments		
SACC	**SACC COMMENTS:** Table E-1 releases were in pounds/year and Table E-2 releases were in kg/day. One or the other unit of measurement should be used.	EPA has revised the Risk Evaluation to provide a summary of the releases in the body of the document in kg/year. The appendix Table E-1 summarizes data as reported to EPA and found in the Pollutant Reporting Tool. Table E-2 converts the lb/year to kg for use as model inputs for E-FAST2014.
SACC	**SACC COMMENTS:** • On p. 22, line 828, the quote regarding the CPSC ban for CCl4 is stated as: "excluding unavoidable residues not exceeding 10 ppm atmospheric concentration." This is not correct. The proper quote is provided on lines 1073-1076 (p. 30) of the draft risk evaluation. Recommendation: Fix the quote regarding the CPSC ban for CCl4 on p. 22.	The regulation is quoted correctly in the final risk evaluation. The regulation is also correctly paraphrased (without quotation marks) throughout the document.
SACC	**SACC COMMENTS:** • There are formatting issues with Table 4-13 (pp. 160-163) that make it difficult to read, and there is a lack of correspondence between some of the row across columns.	EPA considered many of the editorial suggestions and comments provided by the SACC and the public and revised the risk evaluation for clarity. EPA is also considering improving the cancer risk figures in future risk evaluations.

	• Figures 4-1 to 4-4 (pp. 156-157) could be made clearer by using stacked bars rather than parallel bars. Recommendation: Correct the formatting issues with Table 4-13 and improve clarity of Figures 4-1 to 4-4.	
SACC	**SACC COMMENTS:** The SACC provided several editorial comments: • On p. 24, there is a "Section 0". • The title of U.S. EPA, 2019b (*i.e.*, "Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment") should be changed to "Draft Risk Evaluation for Carbon Tetrachloride Supplemental File: Occupational Exposure Assessment" as shown in HERO. • Table 3-10: According to Nagano et al. (2007a), 31 male mice in the 125-ppm group had a pheochromocytoma, not 32. • Line 4177: It seems that the Nagana et al. (2007b) reference should be Nagana et al. (2007a). • Paragraph beginning on line 4202: How is "slope" defined in this paragraph? • Line 4321: The "MS-combo model" is not defined. Perhaps the approach in Chiu and Crump (2012) could prove useful in combining the risk from liver and adrenal tumors. • It is recommended that the entire document be reviewed to ensure that all notation has been clearly defined and is used properly. • Line 800: The same sentence is repeated in this spot. • Table 2.3 needs a reference to Cherrie et al. (2004) (if that is what was used in developing the table). • On line 2143, "Cherrie" is misspelled, and a complete citation is needed. • Page 53, lines 1687-1695: The calculations for dermal	EPA considered many of the editorial suggestions and comments provided by the SACC and the public and revised the risk evaluation for clarity.

	occupational exposure without PPE are not explained, but it is said that "Dermal exposure assessment is described in more detail in Appendix E of the document *Risk Evaluation for Carbon Tetrachloride Supplemental Information on Releases and Occupational Exposure Assessment*" (US EPA, 2019b). When a reviewer tried to access this information, Appendix E was not found in that supplemental document. The reference for the dermal assessment needs to be corrected. • Table 4-13, p. 161 of the draft risk evaluation contains several formatting issues.	
30	**PUBLIC COMMENTS:** There appears to be a typographical error in lines 7020, 7023-7025, which state, "Therefore, the amphibian 9-day lowest LC_{50} of 0.09 mg/L and LC_{10} of 0.037023 mg/L were used to derive an acute COC in Appendix Section G.5 and chronic COC in Appendix Section G.6." In reviewing the original literature (HERO ID 3616521), it appears the LC_{50} values were reported over the range of 0.90-2.83 mg/L for CCl4. Given that 0.90 mg/L is the lowest reported value from that range and used by EPA in developing the acute COC, the appropriate acute LC_{50} for the most sensitive species [Pickerel Frog] is 0.90 mg/L or 900 µg/L. That value divided by an AF of 10 results in an acute COC of 90 µg/L, which seems to be appropriately used in the rest of the risk evaluation. In Appendix Section G.5, lines 7066-7067, the acute COC appears to use the correct value, *i.e.*, the "acute COC = (0.9 mg/L)/(AF of 10) = 0.09 mg/L x 1,000 = 90 µg/L or 90 ppb."	The error in Appendix F (Formerly Appendix G.3) has been corrected. 0.90 mg/L was the lowest reported acute toxicity value and was used by EPA to derive the acute COC (acute COC = 0.9 mg/L/AF of 10 = 0.09 mg/L x 1,000 = 90 µg/L or 90 ppb).

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